FERMENT TREATMENT OF CANCER & TUBERCULOSIS

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THE FERMENT TREATMENT

OF

CANCER AND TUBERCULOSIS.


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THE FERMENT TREATMENT

OF

CANCER AND TUBERCULOSIS.

BY

HORACE MANDERS, F.R.C.S., M.D.

'Science alone is pure: its duty is to prove, not to persuade or convert.'

'Our planet, believe me, labours at some profound work. Do not pronounce rashly upon the inutility of such and such of its parts.'

ERNEST RENAN.

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THIS BOOK IS DEDICATED,

WITH THE GRATITUDE OF THE AUTHOR FOR

MUCH HELP AND ENCOURAGEMENT IN

HIS RESEARCHES.

PREFACE.

It has been my object in writing this little volume to introduce to English readers the theory and practice of the therapeutic employment of pure ferments, first propounded and practised by De Backer. As yet there has been no literature upon the subject in the English language, with the exception of an occasional paper in the medical journals.

It was my intention at first to have translated the large work by De Backer, but I found that as a mere translation it would not be sufficiently concise to be acceptable to the English taste; but I have very freely availed myself of its contents, especially as regards the parts dealing with the earlier work immediately following Bruhat's discovery of the phagocytic properties of yeasts and De Backer's subsequent experiments on animals.

I have thought fit to lead up to my subject with a slight sketch of the general physiology of our bodies, as many of those engaged in the active treatment of disease will have learned their physiology before bacteriology had become a recognised science. A glossary is also added, as so many new words have come into use during the last few years.

The illustrations are faithful reproductions of drawings that I have made from slides prepared in my own laboratory; the slide from which the coloured plate was made is still in my possession, and my thanks are due to the artists who have executed the work so well, also to those friends who have assisted me with the text and proofs.

The reasons that have induced De Backer and myself to employ this treatment in seemingly widely different diseases are all stated in their proper places. We endeavour to effect a cure by the reinforcement of the natural defenders of the body, which has to maintain a struggle against many enemies by the one means given to it.

33, Gloucester Terrace,
June, 1898.

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GLOSSARY.

Actinomyces, plural Mycetes (*ἀκτίς*, a ray; *μύκης*, fungus): The ray fungus.

Adenitis (*ἀδήν*, a gland): Inflammation of a gland.

Aerobic (*ἀήρ*, air; *βίος*, life): A term applied by Pasteur to those entities which require free oxygen for their growth.

Alexines (*ἀλεξειν*, to help): Unstable albuminoid compounds, poisonous to bacteria, secreted principally by the leucocytes.

Alveolus (Lat.): A small cavity or space.

Amphoric (*αμφορεύς*, a jar): Relating to a vase in shape or resonance.

Ampulla (Lat., a flagon): Any body having a similar shape to a jar.

Anaerobic (*vide* Aerobic): Entities not requiring oxygen.

Analgesic (*ἀ*, priv.; *ἀλγέω*, I suffer pain): (1) Having no sense of pain; (2) possessing the power of relieving pain.

Anastomosis (*ανα*, upon; *στομα*, a mouth): The junction of vessels of a similar nature, such as arteries.

Aphthæ (*ἅπτω*, to inflame): Thrush.

Apnœa (*ἀ*, priv.; *πνέω*, I breathe): Absence of air; cessation of respiration.

Ascites (*ἀσκὸς*, a leathern sack): Dropsy of the abdomen.

Ascomyces (*ἀσκὸς*, and *μύκης*, fungus): A fungus which contains endogenous cells.

Ascospore (*ἀσκὸς*, and *σπόρος*, a seed): An endogenous cell.

Autoclave (*αὐτὸς*, itself; *clavis*, a key): An apparatus for sterilization under steam pressure.

Auto-intoxication (*ἀυτὸς*, self; *τοξικόν*, poison): Poisoning of the individual by the accumulation of waste products formed within the body.

Beggiatoa (*J. Beggiato*, an Italian botanist): A species of water fungus.

Bronchophony (*βρόγχος*, the windpipe; *φωνὴ*, the voice): The increased resonance of a patient's voice—heard by the auscultator in abnormal situations—in disease.

Butyric (*βους*, a cow): Relating to butter.

Calcification (*calx*, chalk): Conversion of a structure by a deposition of lime salts.

Cerevisia (*Ceres*, Lat.): A fermented fluid made from grain; beer.

Carreau (Fr.): A term applied to a square, hard, tumid condition of the abdomen seen in children.

Caseation (*caseum*, cheese): Conversion into a yellow, cheeselike substance.

Chemiotaxis (*χημεία*, chemistry ; *ταξίς*, order) : Chemical affinity or repulsion, exercised by cells.
Chlorophyll (*χλωρός*, green) : The green colouring matter of plants.
Cholesterine (*χολή*, bile ; *στερεός*, solid) : A substance found in the bile and in fat in the form of thin rhombic plates containing detritus, etc.
Chromogenic (*χρωμος*, colour ; *γεννάω*, I produce) : Possessing the power of generating colour.
Cilia (*cilium*, an eyelash) : Vibratile hairlike fringes on cells, found chiefly in the air-passages.
Cladothrix (*κλάδος*, a branch ; *θριξ*, a hair) : A species of water fungus, which gives rise to a form of phthisis which is very rare.
Coccus (*κόκκος*, a berry) : A genus of the pathogenic fission fungi, occurring in the form of spherical or oval-shaped cells.
Coryza (*κόρυς*, the head) : A catarrh or cold in the head.
Crenellated (*crena*, a notch) : Indented in the circumference.
Crepitation (*crepitare*, to crackle) : Fine crackling like that of hair.
Dextrose (*dexter*, right) : Glucose, which turns the plane of polarization to the right.
Dextrine : Soluble gummy matter formed from starch by diastase.
Diapedesis (*διὰ*, through ; *πούς*, a foot) : The passage of leucocytes through the wall of a bloodvessel into the surrounding tissues.
Diaphoretic (*διὰ*, through ; *φορεω*, I convey) : Remedies which increase the secretion of sweat.
Diastasic (*διὰ*, through ; *στασις*, a separation) : Possessing the power of converting starch into glucose.
Diastole (*διαστολή*, a drawing apart) : The passive, normal dilatation of the heart.
Diathesis (*διατίθημι*, I dispose) : A constitutional tendency.
Diuretic (*διὰ*, through ; *οὐρέω*, I pass water) : Increasing the flow of urine.
Dynamogenic (*δυναμις*, force ; *γενναω*, I produce) : Producing energy.
Dyspnœa (*δύς*, with difficulty ; *πνέω*, I breathe) : Difficulty in breathing.
Efferent (*effero*, I bear away from) : Outflowing.
Encapsulation (*capsula*, a capsule) : The development round some foreign body or product of disease of a fibroid limiting membrane.
Endogenous (*ἔνδον*, within ; *γενναω*, I produce) : Reproduction within a cell.
Endothelium (*ἔνδον*, and *θαλλω*, I grow) : The lining cells of an internal membrane.
Encysted (*ἐν*, in ; *κύστις*, a bladder) : Confined by a saclike membrane.
Enzyme (*ἐν*, in ; *ζυμόω*, I ferment) : Soluble ferments possessing neither substance nor shape.
Epithelium (*ἐπὶ*, upon ; *θάλλω*, I grow) : The most superficial cells of the skin or mucous membrane.
Epithelioid (*ἐπὶ*, *θάλλω*, and *ειδος*, like) : Resembling epithelium.
Epistaxis (*ἐπὶ*, upon ; *σταζω*, I drip) : Bleeding from the nose.
Exanthemata (*εν*, out ; *ἀνθέω*, I blossom) : A group of contagious diseases characterized by rashes.
Flagella (Lat., a whip) : A fine whiplike process.
Fremitus (Lat., a murmur) : A trembling or quivering elicited by placing the hand over the respiratory organs while the patient speaks.
Furunculosis (Lat., a boil) : A state of health characterized by boils.

Germicidal (*germa*, a germ; *cædere*, to kill): Possessing the power of killing germs.
Gregarinida (*grex*, a herd): A class of Protozoa.
Hæmostatic (*αἷμα*, blood; *στάσις*, standing): Possessing the power of arresting bleeding.
Hyaline (*ὕαλος*, glass): Having the appearance of ground-glass or wax.
Hygroscopic (*ὑγρος*, moist; *σκοπέω*, I see): Having the power of absorbing moisture.
Hyphæ (*ὑφη*, a weaving, a web): The threadlike appearance of the mould fungi.
Hyphomyces (*ὑφη*, a web; *μύκης*, fungus): Mycelial fungi of a branching form.
Hypostasis (*ὑπο*, beneath; *στάζειν*, to drip): Sinking of the blood or lymph to the most dependent part.
Indican (*indicum*, indigo): A natural glucoside found in indigo.
Infarction (*infarcere*, to fill in): A wedge-shaped area resulting from plugging.
Infundibulum (Lat., a funnel): The part of the lung leading from the terminal bronchi to the air cells.
Intercostal (*inter*, between; *costa*, a rib): Lying in the space between the ribs.
Invertine (*invertere*, to place in a contrary position): A ferment which converts cane-sugar into invert-sugar with the properties of glucose.
Karyokinesis (*κάρυον*, a kernel; *κίνησις*, movement): The changes which take place in a nucleus when a cell is about to divide.
Lacuna (*lacus*, a lake): A little hollow
Leptothrix (*λεπτός*, thin; *θρὶξ*, a hair): A fission fungus with thin branching threads.
Leucine (*λευκος*, white): A product of pancreatic digestion.
Leucomaines (*λέυκωμα*, white of egg): Substances the result of tissue metabolism.
Leucocyte (*λευκος*, white; *κύτος*, a cell): The white cells of the blood, etc.
Leucocytosis: A temporary multiplication of leucocytes in a part.
Macrophage (*μάκρος*, big; *φάγω*, I eat): Large-sized phagocytes.
Magma (*μαγμα*, a mass): A pulpy mass.
Medullary (*medulla*, marrow): Resembling marrow
Mesenteric (*μέσος*, middle; *ἐντερον*, bowel): Having to do with the mesentery.
Mesentery: The membrane which supports the small intestines, and contains their bloodvessels.
Metabolism (*μεταβολή*, change): The vital change that occurs in tissues.
Metachromic (*μετα*, beyond; *χρωμος*, colour): Play of colours.
Micrococci (*μικρός*, little; *κόκκος*, a berry): Synonym for cocci.
Microphage (*μικρός*, and *φάγω*, I eat): Small-sized phagocytes.
Miothrix (*μεῖων*, less; *θρὶξ*, a hair): A species of the higher bacteria.
Mucorineæ (*μύκης*, fungus): Moulds.
Mycelia: Mould fungi in a congeries of hyphæ.
Necrosis (*νεκρός*, death): The death of any limited portion of the body.
Nematodes (*νηματωδης*, threadlike): Applied to certain parasitic worms within the intestines.

NEUTROPHILE (*neuter*, neither; *φίλος*, loving): A term applied to cells which do not stain easily with either acid, neutral, or alkaline dyes.

NEURASTHENIA (*νεῦρόν*, a nerve; *ἀ*, priv.; *σθενός*, strength): A morbid condition of the nervous system.

NUCLEIN (*nucleus*, a kernel): The active principle contained within the true nucleus—very resistant to all reagents.

NUCLEOLUS (Lat.): A smaller body situated within the true nucleus.

PALPATION (*palpare*, to feel): A means of diagnosis by touching or feeling with the palm of the hand.

PARENCHYMA (*παρὰ*, beside; *ἐνχειν*, to pour in): The fundamental tissues of solid organs.

PATHOGNOMONIC (*πάθος*, disease; *γνώμον*, a sign): Indicating the presence of certain pathological conditions.

PECTORILOQUY (*pectus*, the chest; *loqui*, to speak): Articulated sounds made by the patient, which are conveyed by the stethoscope directly into the ear of the auscultator.

PEPTONES (*πεπτειν*, to digest): Albumins that have been prepared by the digestive ferments for absorption into the system.

PERISTALTIC (*περί*, around; *σταλσις*, constriction): A wavy contraction of the muscles around a circumference.

PHAGOCYTES (*φαγεῖν*, to eat; *κύτος*, a cell): Cells which have the power of inglobing particles.

PHAGOCYTOSIS: The power possessed by phagocytes of inglobing microbes and other bodies, these being often digested.

PHYLAXINES (*φύλαξ*, a guard): Matters, protective against microbes, secreted by cells within the economy; a kind of alexine.

PNEUMOLITH (*πνευμων*, the lung; *λίθος*, a stone): A concretion formed in the lung.

PSEUDOPODIA (*ψευδὴς*, false; *πῶυς*, a foot): Tendril-like expansions thrown out by leucocytes.

PNEUMOTHORAX (*πνεῦμα*, wind; *θώραξ*, the chest): The presence of air within the pleural cavity.

PTOMAINES (*πτῶμα*, a dead body): Toxines, allied to vegetable alkaloids, formed by the decomposition of dead bodies by saprophytic microbes. Most ptomaines are very poisonous.

PYOGENIC (*πυον*, pus; *γεννάω*, I produce): Pus-forming, a term applied to certain microbes.

SACCHAROMYCES (*σάκχαρον*, sugar; *μύκης*, fungus): The sugar fungus, or yeast, of which there are many kinds.

SAPROPHYTES (*σαπρός*, decay; *φυτόν*, a plant): Fission fungi, which derive their nutriment from dead organisms, or from solutions of organic matter.

SARCINÆ (*sarcina*, a bundle): A bundle of cocci, containing cubes of four, found in certain diseases of the stomach.

SCHIZOMYCES (*σχίζω*, I cleave; *μύκης*, fungus): Fission fungi.

SCLEROSIS (*σκληρος*, hard): A term applied to any tissue that has become hardened by disease, the elements being gradually replaced by fibrous tissue.

SEPTATE (*septum*, a fence): Possessing partitions.

SINUS (Lat., a canal): A suppurating tract leading to a diseased part.

Sordes (*sordere*, to be foul): An accumulation about the lips and teeth of a blackish substance, containing particles of food, micro-organisms, etc., found in severe cases of fever.

Sozines (σωζειν, to save): A kind of alexine.

Spirometer (σπιρός, breath; μετρέω, to measure): An instrument for measuring the quantity of air contained in the lungs.

Staphylococci (σταφυλή, a bunch of grapes): A collection of cocci resembling a bunch of grapes.

Streptococci (στρεπτός, a chain): Cocci that adopt a chainlike formation.

Streptothrix (στρεπτός, a chain; θρὶξ, a hair): Higher bacteria of a form resembling chains of fine hairs.

Succinic (*succinum*, amber): Pertaining to amber.

Symbiosis (συμ, together with; βίος, life): A harmonious community of existence; microbes of different species existing together in a part.

Systole (συστολή, a drawing together): The contraction of the heart.

Tetracocci (τέτρας, four; κόκκος, a berry): Cocci that exist in double pairs.

Thrombosis (θρόμβος, a clot): The development during life of a clot within a bloodvessel.

Teletyptic (τελε, from afar; τυπτω, to strike): A term applied to toxines, which act injuriously upon the tissues at a distance from the bacteria which produce them.

Toxalbumin (τοξικόν, poison; *albumin*, white of egg): An active albuminoid substance, excreted by bacteria.

Triatomic (*tres*, three; *atomus*, an atom): Possessing three atoms.

Tympanitic (*tympanum*, a drum): Like a drum in regard to hollowness or tenseness of membrane.

Tyrosin (τυρός, cheese): One of the products of the waste of proteid matters.

Vacuole (*vacuolum*, a little empty space): A tiny space, or minute drop of fluid, in the protoplasm of a cell.

Velum (Lat., a veil): The soft palate; a hanging partition.

Vibrio (*vibrare*, to vibrate): A bacterium which is curved or wavy in shape, and not straight, such as the comma bacillus of cholera and that of relapsing fever.

Xanthin (ξανθός, yellow): Urous acid, a leucomaine found in all tissues of the body, and in the urine.

Zyme, Zymotic (ζυμόω, I ferment): Bodies, formed or not, that have the power of causing fermentation.

Zoogloea (ζωον, an animal; γλοιός, a sticky substance): A glutinous mass of bacteria.

THE FERMENT TREATMENT

OF

CANCER AND TUBERCULOSIS

CHAPTER I.

INTRODUCTION.

The treatment of disease by pure ferments being a new departure in the domain of therapeutics, it will be imperative upon us to render a clear explanation of their action without the animal body, and more especially within it.

As their action within the economy so strongly resembles that of certain cells naturally existing there, to which the power is given of defending it against disease, of restoring it after disease, and even of repairing it after injury, a short sketch of the composition and function of some of the constituents of the human body will form a useful preliminary to our work. Following this will be described what ferments are and how they act.

By this means we shall be the better enabled to comprehend not only the theory of the treatment, but its practical soundness and utility. When we have acquired this knowledge, we shall then get an insight as to what kind of disease is likely to be arrested or cured by pure ferments, and, lastly, we shall find no difficulty in comprehending how it is that

certain diseases seemingly quite opposed to each other in their pathology may yet be equally obliged to yield to their influence.

The tissues that go to make up the body, whether they be hard and dense, such as bone and cartilage, of varying degrees of softness, such as muscles, liver, etc., or fluid, such as the blood and lymph, all consist of cells or cells elongated into fibres, bathed in a certain amount of liquid. In the case of the denser structures this amount is exceedingly small, whereas in the fluid structures it may be greater than that of the cells. These cells are arranged in different shapes and patterns to form organs, each of which has its own particular pattern to enable it to perform its own particular function; these functions, either of excretion, secretion or metabolism, are performed actually by their individual or intrinsic cells, which have gradually acquired the special knowledge and power of so doing during the course of countless generations proceeding through æons of time. This power is increased and still further differentiated as it is handed down from generation to generation : the process is still going on ; there is no standing still, consequently it may happen that future ages will see the perfect development and acquirement of new functions in certain cells of the brain, the outcome, perhaps, of the humble and infinitesimal beginnings generated by the efforts of the thinkers and brain-workers of to-day.

It seems extraordinary that such a complex whole as is the human body can be built up from one type only, that of a single cell. Yet it is so, and it is maintained, nourished, and even repaired, by cells also. I have just mentioned the human body, but I do not thereby exclude other bodies, for everything that has life, whether animal, vegetable, or possessing some of the attributes of both, is either a simple cell in itself or a more or less complex collection of cells.

Let us, then, study for a little while what is a cell. This may be said to be a minute portion or little speck of living

substance resembling gelatine in appearance and stickiness. This material is called protoplasm, from two Greek words which mean 'the first substance moulded' or brought into form. The protoplasm of a vegetable cell is enclosed within a delicate envelope, or cell membrane, but this is very rarely, or never, the case with animal cells, or it may be that it is too fine and delicate to be distinguished. Almost all cells contain within them an object which appears like a smaller cell. This is invariably enveloped in a membrane, and is termed the nucleus (kernel). There may be only one or several nuclei within a cell, and these nuclei may contain within them certain bright bodies called nucleoli. These will be referred to presently.

The protoplasm of a cell consists of a substance (muco-globulin) which is very similar to albumin in its chemical constituents, and very like gelatine, as we have said, though it is not always quite clear, but may present a granular appearance to the eye. This is due to the fact that the protoplasm is not entirely homogeneous, or made up of the same structure. This is made apparent by a higher magnification under the microscope and staining reagents, whereby we find that two distinct structures are present, one of which is reticulated like a network ball or a sponge with more holes than substance, from which it has received the name of spongioplasm ; the other substance is clear and transparent, hence it is called hyaloplasm, from a Greek word meaning 'glass.' This substance possesses the peculiar property of projecting itself outside the spongioplasm, and of flowing around any substance that may come in its way ; it then withdraws itself into the spongioplasm, taking with it the acquired foreign substance, holding it, and never quitting it, if a solid particle, until the death of the cell, but it may be thrown out as a waste product of digestion when the cell chooses, should the particle inglobed have been of an organic nature. This incorporation of solid particles within the cells is well seen in the case of

tattooing, which is permanent. The flowing movement of the hyaloplasm is specially well seen in certain cells, such as the leucocytes, or colourless cells of the blood; these throw out long processes of hyaloplasm like the tentacles of an octopus, and along one of the tentacles, or pseudopodia, as they are termed, the spongioplasm is enabled to flow, for it is quite elastic and able to adapt itself to any shape: hence by this alternate projection and concentration in the new direction, a kind of progression occurs which has been termed the 'amœboid movement, on account of the close resemblance it bears to that adopted by the amœbæ, which are microscopic animalcules of the most primitive type.

By means of this gliding movement the leucocytes are enabled to traverse seemingly solid structures, through whose walls they pass by insinuating themselves between the various layers and the very cells of those layers; they may then wander at will, or perhaps lie dormant within the connective tissue. This traversing movement is called diapedesis, and is so performed that in the healthy state not a drop of fluid escapes with the cell unless it is desired that it should be so.

The nucleus of a cell, as we have said, is always surrounded and enclosed by a membrane; this membrane is connected throughout by bands or fibres of various thicknesses, passing from one part of its inner periphery to another; this is called the intranuclear network, and represents what in a higher entity would be the skeleton. At a certain point or points of this network appear enlargements; these are called nucleoli. This framework or skeleton, consisting of investing membrane, intracellular network and nucleoli, stains easily and deeply with most dyes, hence it has received the name of chromoplasm, and its fibres are called chromatic.

All tissues of the body require new material for their nourishment and growth, as well as for the maintenance of their special functions, from a supply of raw material; equally essential is it that their waste products be removed. When these

processes are harmoniously balanced, the body is then truly in a state of health. It stands to reason that the cells which compose the fixed tissues of the body—bones, muscles, heart, lungs, liver, etc.—cannot go and fetch material for themselves, hence it follows that carriers must be provided for them, and certain cells of the fluids of circulation are told off for that purpose. They are found in the streams of the blood and of the lymph, and are here known as corpuscles ; they are of the red and white variety, but although the blood-current contains both kinds—but chiefly the red, in the proportion of nearly 500 to 1 of the white—the lymph-current contains white corpuscles only. The fluid that bears them, however, is practically identical ; hence blood may be said to be lymph containing red corpuscles, and lymph may be appropriately termed blood deprived of them. There is a slight difference which varies, as does also the plasma of the blood, for the lymph, even including the lymph in the mesenteric vessels, is a stream proceeding from the tissues, consequently it must contain certain products of waste. To a certain extent this is also true regarding venous blood, though to a very much less extent. The arterial stream, on the contrary, conveys new material dissolved within it to the tissues, yet is not without waste product even then, as evinced by the excretion of the kidneys.

First let us trace the function of the blood with its red cells, after it has been thrown into the general circulation by the left side of the heart, every red cell brim full of oxygen, the plasma or fluid enriched with new material. It travels along the arteries, which gradually diminish in size until they become so small that they do not need the firm coating with which they were originally supplied, consequently they are modified into vessels called capillaries, from their extreme fineness. Arrived here, the blood moves much more slowly, in order to give more time to the corpuscles, which in the slackened stream are able to part with their oxygen to the

cells of the tissues that require it, receiving carbonic acid in exchange. As the stream flows onwards, and the interchange is effected, the capillaries gradually change their character, and become larger, until they are indistinguishable from small veins. When this point is reached, the rate of current is again accelerated.

During the period that the circulation is retarded within the capillaries, a certain proportion of the fluid of the blood exudes through their thin walls into the surrounding tissues, thus bathing the cells of which these tissues are composed, and yields up to them those soluble matters which they need, each according to its kind, and consequently select out of it. The fluid, thus denuded, does not return to the blood-current in the capillaries, but enters the lymphatics, which are vessels which arise by open mouths or spaces within the tissues, gradually adopt a more definite structure with a distinct lining, and finally run into glands, within which a species of filtration takes place. The lymph-stream, thus purified, flows on mechanically, either through other glands or not, but in any case into large lymphatic trunks, which pour their contents into the junction of the large veins at the root of the neck. The lymph thus passes into the venous stream, and is carried with it directly into the heart, whence it is immediately pumped into the lungs.

The large lymphatic duct on the left is much larger than its fellow on the right, for, in addition to receiving the lymph-stream from the lower limbs and abdominal organs, it also receives the whole of the chyle absorbed in the intestines from the food elaborated therein, and rendered thereby fit for absorption. This is taken up by the open mouths of these lymphatics, here termed lacteals (from the milky appearance of their contents), and poured into a receptacle from which this large trunk, called the thoracic duct, arises. It is through this that the blood obtains almost all the nutriment for the body generally, together with a portion of its waste. Some

of the nutritious elements from the food, however, get directly into the circulation, and proceed to the liver, as we shall see when we come to speak about diabetes. On account of the waste products within it, the blood has to be cleaned, which duty is performed by the lungs, the skin, and the kidneys, each of them possessing their own peculiar attributes, yet having the power of assisting each other, should one of them become disabled.

The red blood cells are minute, biconcave discs, resembling coins with very thick edges, like the pre-Victorian pennies. They are like coins in another respect also, for they have a tendency to run together like rouleaux. They only measure about the $\frac{1}{3200}$ of an inch in their greatest breadth, but are exceedingly numerous, 1 cubic millimetre containing about five millions of them. They are of a pale yellow colour under the microscope, although the blood is red, owing to the great number of them in that fluid. In substance these red corpuscles are soft, homogeneous and elastic, for if pressed out of shape, they rapidly regain it when the pressure is removed. They do not appear to be possessed of a limiting membrane, neither have they any nucleus (in mammals). They contain a peculiar ferruginous principle called hæmoglobin, which normally exists in two forms, which differ as to the quantity of free oxygen they contain.

When the blood has been pumped from the heart into the lungs, it there meets with free oxygen, which is at once seized upon by the hæmoglobin, with which it enters into a loose combination, thereby acquiring that bright red tint seen in arterial blood, and in the frothy expectoration of acute hæmoptysis. After the oxygen has been acquired in the lungs, the charged corpuscles are carried in the blood-stream to the left side of the heart, which immediately sends them forth with the fluid surrounding them into all parts of the system. On reaching the capillaries they are introduced by the slackened current to tissues that require oxygen, but can-

not fetch it for themselves. When they have received carbonic acid in exchange, they speedily return by the veins to the lungs, there to yield up their burden of waste, and again acquire a fresh consignment of oxygen. These interchanges are effected within the capillaries, for in health the red cells never quit their vessels.

Now we see that the fluid of the blood carries soluble food, acquired from the lacteals, in the shape of proteids, carbohydrates, fats and salts, as well as the waste products of exchange, which are returned by the lymph, as already explained, also that the red cells carry oxygen or carbonic acid, as the case may be. These interchanges of nutrition, repair, and waste are all grouped under the term metabolism, from a Greek word meaning 'change.'

The white cells, colourless corpuscles, or leucocytes, are typical cells, as we have already described. They play quite a different part to that played by the red corpuscles, for these leucocytes are not common carriers, nor do their functions seem limited to any one particular business; they seem endowed with an intelligence entirely their own, wander about or rest at will, and appear to exert a watchful and preservative action over the economy, exercising the duties of foremen of works and of police; they multiply by division, and are chiefly formed in the spleen and lymphatic glands; they are capable of repairing any tissue that may accidentally get injured. Should bacteria invade the system, they rush to the point of invasion, and repulse the attempt by inglobing and digesting the invader if not strong, or fighting and wrestling with him if strong and numerous, many of them dying in the struggle; these may be absorbed, but if numerous they undergo coagulation necrosis, by which their shape becomes altered, and are eliminated from the system as pus cells.

Their powers do not end here, for whether existing as leucocytes in the blood, wandering through the vessel walls

into the tissues, or lying dormant within them, they are capable of secreting within their protaplasm soluble substances which are excreted into the lymph or blood stream, thus protecting the system from the poisonous effects of the waste products of metabolism (leucomaines).

In disease these secretions are intensified, and are called alexines; they are modifications of the nucleins, or active chemical constituents of the nuclear matrix and hyaloplasm of cells. Nuclein is a muco-globulin containing a very considerable quantity of phosphorus, as will be seen by the subjoined analyses :

From Leucocytes.	From Brain.	From Yeasts.
C = 49·58	C = 50·06	C = 29·00
H = 7·10	H = 7·60	H = ·49
N = 15·02	N = 13·18	O = 32·00
P = 2·28	P = 1·89	P = 6·00

Leucocytes contain several proteids, an alkaline albuminate, a proteid that coagulates at 48° C., another resembling myosin, also paraglobulin, peptone, a coagulating ferment, and nuclein.

One of the objects of this work will be to show that other bodies (cells) possess virtually the same chemical constituents, the same inglobing attribute, and the same power of neutralizing or destroying the products of bacteria. These cells are derived from the family of the Saccharomyces, or sugar fungus, commonly known as yeasts.

We shall now proceed to describe them and their functions, first explaining the different kinds of ferment that are met with in Nature.

By the term 'ferment' we mean an agent or body derived from the vegetable or animal kingdom which possesses, under certain conditions, the power of initiating chemical changes and metamorphoses in complex organic substances, and of maintaining the phenomena, provided that the products of the change be removed when formed.

These ferments, or zymes (ζυμόω, I ferment—hence the term

zymotic, as applied to disease), are of two kinds: the first possesses a definite organism and shape or form, from which they are termed 'formed ferments'; the second possesses neither substance nor shape—they are termed enzymes, and are soluble.

Formed Ferments.

These consist of single cells, differing in shape, form, size, and mode of growth, according to the different species to which they belong. They are vegetable cells, classed in the same natural order as that of the Fungi or Mycetes (μύκης, fungus), which are of the lowest order of vegetable life, the formed ferments belonging to the lowest sub-order. Their cells possess a cell wall, or envelope, and are consequently classed as vegetables, although some of them behave so much like animal cells, and have so little in common with vegetable life, as to make us wonder whether here is not probably the link which connects the two kingdoms, constituting what has been happily termed by Michael Foster the 'wavering barrier,' which is indeed a hedge so thin, and containing so many gaps, that often we really cannot tell upon which side we are standing.

The following properties are invariably possessed by formed ferments:

1. Of being organized nitrogenous compounds.
2. Of being endowed with life, *i.e.*, of being unstable, and capable of having their powers impeded by chemicals and other causes.
3. Of being able, whilst in relatively small proportion to the substance acted upon, to produce great changes in that substance.

They may be arranged in three groups: (1) The Moulds, mycelial fungi, or Hyphomycetes; (2) the Yeasts, sugar fungi, or Saccharomycetes; (3) Bacteria, fission fungi, or Schizo-

mycetes. Most of the members of the first group, and all those of the second and third, are capable of setting up the phenomenon called fermentation, when in suitable media and conditions.

I. THE MOULDS.

The moulds, which are usually seen upon the surface of food, fruit, wood, etc., when left in a damp atmosphere, are usually agents of disintegration and putrefaction. Some of them are pathogenic, more usually to the exterior of mankind, such as those to which the diseases called favus and ringworm are due. As an exception to this, there is the terrible Actinomyces, which is difficult to class, as it possesses many of the attributes of moulds, such as forming a mycelium, whilst in other respects it resembles the higher bacteria. Moulds propagate by spores or conidia, which are very resistant to heat or chemical reagents. This group is divided into four sub-orders, according to the arrangement of their seed-bearing organs.

It is the first sub-order, that of Mucorineæ, which chiefly concerns us here, for it is principally members of this division that set up chemical metamorphoses in saccharine liquids. They hinder and spoil the action of the true sugar fungus, if in any quantity ; they will also grow and feed upon yeast that is exposed to the air.

II. THE YEASTS.

The yeasts are a group of organisms which, under the microscope, appear round, oval, elliptical, some of a peculiar sausage-like shape, and others like an amphora or a medlar fruit. They are little membranous bags with the characteristics of vegetable cells, generally reproducing themselves by gemmation or budding, the buds resembling the spores of fungi, and are consequently termed conidia. Under certain conditions these conidia form chain-like hyphæ, and under other conditions may form endogenous spores (ascospores).

There is a large number of different species of yeasts, some species containing numerous varieties. The *Saccharomyces ellipsoideus* is an important agent in the fermentation of wine, while the *Saccharomyces cerevisiæ* is the most important in that of beer, or in the fermentation of malt for the distillation of spirit. Of these two species there are innumerable varieties, which are not capable of being differentiated, even under the microscope, but which give rise to the various bouquets and characteristics generally of the products of the

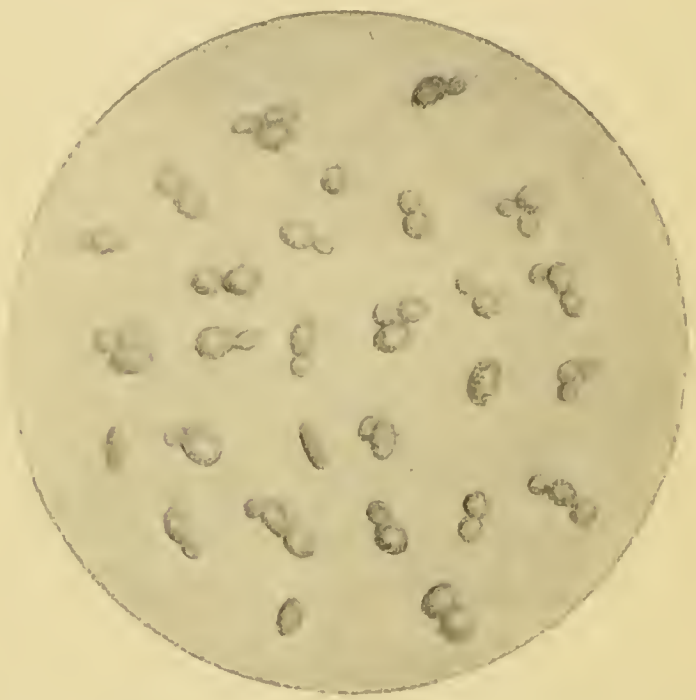


FIG. 1.—YEASTS FROM THE GRAPES OF CLOS VOUGEOT.

Yeasts of wine taken from the celebrated vineyard of Clos Vougeot, Burgundy.

vintages and breweries to which they belong. In vinification, these wine yeasts have of late years been jealously guarded, as it has become known that if the products of Australian or Californian vineyards were fermented with yeasts from Clos Vougeot or Château Margaux (Fig. 1), the wines from the New World, already noted for their purity and excellence, would acquire the bouquet and flavour of these celebrated vintages. Other yeasts, such as are no good in the great industries of wine or beer making, but are harmful and deleterious to such,

are termed wild-yeasts, just as we apply the term to certain flowers that grow without care and attention, and consequently, with certain exceptions, do not possess either the fragrance or beauty of those that are carefully selected and encouraged.

Certain years are well known for their excellent vintages, but not necessarily for all wines. There are champagne years, such as 1874, port years, as 1847, claret years, etc.; and, although much may be attributed to the weather affecting the development and ripening of the grapes themselves, later researches will show that the purity and quality of the yeasts naturally deposited upon the stalks and grapes have far more effect upon the quality of the vintage than was formerly suspected, and that, as these perfect yeasts will be now preserved for future use in vinification, the growers will be able to obtain a much better average in the excellence of their wine than was otherwise possible.

A very few years ago brewers were much disheartened by the results of an entire brewing frequently going wrong, seemingly without cause, and large sums of money were offered to anyone who could discover the cause, and so find a remedy. One of the largest brewing firms in the world would never lay in any fresh plant until absolutely obliged, for fear of any such accidents happening, as it was felt that such an occurrence must be due to some outside influence. It is now known that these accidents were due to the action of wild-yeasts, which caused the beer to become thick, ropy, acrid, and bitter.

It is to the researches of Hansen of Copenhagen on brewer's yeast, and those of Jacquemin of Nancy on the ferments of wines, that we owe most of our present knowledge. The facts cited above have been adduced to point out the necessity of obtaining absolutely pure cultures from a good strain when dealing with the properties of yeasts; the application of these principles will be pointed out in their proper places in succeeding chapters. The most common wild-yeast is

the *Saccharomyces Pastorianus* (Fig. 2), of which, again, there are several varieties; this one is particularly mentioned because it was in observing this particular variety that M. Bruhat discovered a phenomenon, the application of which to the diseases of man as initiated by Dr. de Backer has led to such wonderful results. For the treatment of disease, however, this wild-yeast was found eventually to be inferior in many ways to the *Saccharomyces cerevisiæ*, which we now use



FIG. 2.—SACCHAROMYCES PASTORIANUS.
The yeast in which inglobement of bacilli was discovered by M. Bruhat.

therapeutically, and to whose morphology and characteristics we shall next turn our attention.

The *Saccharomyces cerevisiæ* appears under the microscope in the form of rounded or oval cells 8 or 9 μ (about $\frac{1}{3000}$ of an inch) in their longer diameter. These present three different forms: (1) Conidia, the shape ordinarily adopted when the cells are vigorous; (2) the Hyphomycetic form, which appears in chains of several elements or conidia placed end to end, but

never appear as a true mycelium nor with spore-bearing hyphæ; (3) a form containing endogenous spores, or Ascomycetes.

1. *Conidia.*—To obtain yeast in this form for microscopic study or for future culture, we make a must or wort of fermentable saccharine material with a proportion of gelatine added, so that at a temperature of 20° to 25° C. it is neither liquid nor solid, but pasty; a thin layer of this is introduced at the bottom of a Petri dish, which is sterilized by heat; when sufficiently cool, the cap is momentarily removed and a speck of pure culture of *Saccharomyces cerevisiæ* is stirred into the mixture at the bottom by means of the platinum wire. It is a good plan to submit the culture to be used to a stream of oxygen beforehand, a plan we always adopt, as will be seen later, when preparing cells for their entrance into the human body. The next step is to place the dish in a recipient full of a neutral gas.

Carbonic acid or nitrogen will do very well (the object of this is to exclude the air), and the whole is left to itself for three or four days, at the end of which time some little white specks can be seen, which are colonies of saccharomyces developing from single cells of the culture introduced. A tiny trace is picked up by the platinum loop, and slides made from it—some stained with various colours, and others in a natural state. On examination we find a number of roundish or oval cells, consisting of a very fine exterior membrane, of which, in the unstained preparations, we can hardly distinguish the inner contour; the interior of this membranous bag is filled with colourless homogeneous protoplasm, often exhibiting one or more colourless lacunæ, called vacuoles, though they may be perhaps simply fat globules. Some of these cells show little buds or gemmations, usually at one, or even both extremities of the long axis; these are the commencing daughter-cells, and careful observation will demonstrate to us several stages of this kind of reproduction. When the cell is about

to bud, we can see a slight point or protuberance in the membrane of the envelope, which gradually increases, and changes its shape from being a simple projection, for it becomes more rounded and pinched in at the base ; the protoplasm of the whole cell is still entire, but later on we can see that, at the pinched-in part, the enveloping membrane is still closing in, and that two distinct protoplasms are present ; next, that an extremely thin membrane, stretching across the narrowing

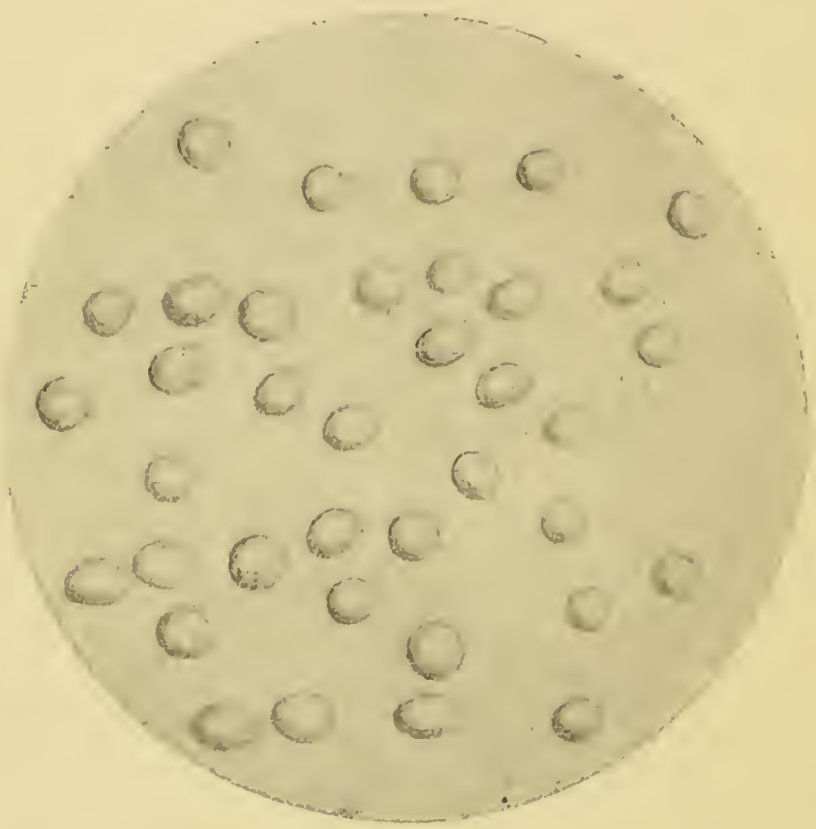


Fig. 3.—Saccharomyces Cerevisiæ (Conidia).

A pure culture such as is used by the Author for hypodermic injection.

part of the cell wall, proceeds to complete the budding cell, which till then has been living at the expense of the mother-cell ; finally the separation is complete, and the daughter-cell has its own distinct existence, even though it may remain yet for some time attached to the envelope of the parent cell, and actually whilst so attached may reproduce by throwing out processes in a similar manner ; it is more usual for it to become entirely detached before doing so. This rotund form of

cell is the one usually seen in the process of anaerobic fermentations of yeast, constituting its more vigorous form. The drawing (Fig. 3) shows a good, clean, vigorous yeast, such as we use therapeutically.

2. *The Chain-like Form.*—To obtain yeast cells in this shape it is necessary to alter the above experiment slightly; the wort is made rather stiffer, with a greater proportion of gelatine, and the dish is exposed to a quantity of sterilized air instead of a neutral gas; in other respects the proceedings are the same. At the end of a day or two the colonies appear as before, and are examined in the same way. This time we shall find that very few of the cells are round or oval, though we shall see some even budding; the majority of the cells, however, will have quite a different appearance, being much more elongated in their long axis, or cylindrical, somewhat like the mycelium cells of the hyphomycetic fungi. Most of these have developed from the extremities of the parent cell, thereby presenting a filamentous appearance; some, on the other hand, have developed laterally, and these daughter-cells maintain the oval shape. In the elongated variety the cell wall appears to be thicker than in the rounded form, but the interior protoplasm is of the same hyaline and homogeneous character.

This hyphomycetic form is only seen when the yeast is grown under aerobic conditions and when the nutrient medium is nearly exhausted of its saccharine. If, however, we place cells of this form in a more nutritious medium and under anaerobic conditions, they acquire greater vigour and take on the oval shape.

Fig. 4 shows the filamentous form as obtained from a culture, and the reader is referred to the coloured plate for a further instance.

3. *Endogenous Spores.*—For the production of this form a different plan must be adopted. Small blocks of well-baked plaster of Paris are placed in a Petri dish, which is half filled

with water, the cover is put on, and the whole sterilized. When cool enough, the cover is removed and the blocks seeded with a trace taken from saccharomyces cells that have been cultivated for some days in an infusion of sterilized malt at a temperature of about 20° C., and the young cells selected and developed in a similar wort for twenty-four hours, at a temperature of 24° C. ; the blocks are then left in the Petri dishes at a temperature of 30° C. for twenty-four hours ; from the eighteenth hour onwards slide preparations may be made from



FIG. 4.—SACCHAROMYCES CEREVISIÆ.
From a film (Hyphomycetic form).

them as before. The first thing that will be noticed is that the cells have increased in size ; then that the homogeneous protoplasm shows vague condensations, which later appear as shining spots becoming more spherical, after which they are invested with a fairly distinct membrane ; finally the endogenous spores are seen, perfectly formed, each one clothed with a well-defined enveloping membrane. In some cells, in which sporulation has been very active, the spores swell and compress each other to such an extent that the cells appear as if

divided into compartments by partitions; the cells usually contain three or four of these new endogenous cells, or ascospores, as they are termed, but sometimes they contain as many as five; their size varies from $2\frac{1}{2}\,\mu$ to $6\,\mu$.

If these cells are introduced into a nutritive medium, they will germinate, the spores distending and thinning the wall of the parent cell, which finally ruptures and remains in a state of volva or loose shrivelled skin, partly enveloping the spores. These latter put out buds, and now behave like conidia in propagating by gemmation; this they have been known to do whilst still within the parent cell, but such precocity is rare.

It has been before stated that the yeast cell consists of a continuous enveloping membrane enclosing a hyaline protoplasm; this membrane is composed of a peculiar kind of cellulose, resembling a vegetable mucilage, insoluble in ammonio-oxide of copper. The weight of the membrane has been estimated at about $\frac{37}{100}$ of that of the dried cell. The hyaline protoplasm is of very complex nature. It is composed of albumin (36 per cent.), peptones, fatty matters (almost entirely olein), extractive matters, leucin, tyrosin, and xanthine (from the destruction of proteids), traces of glucose, glycogen, succinic acid, cholesterin, nuclein and invertin; lastly, of mineral matters (7 per cent.), which are composed of:

	Belohoubek.		*Mitscherlich.*
Phosphoric acid	51·10	...	54 to 59
Potassium	38·68	...	28 to 40
Magnesium	4·16	...	6 to 8
Calcium	1·99	...	1 to 4
Sulphates (soda and silica) ...	4·07		

III. BACTERIA.—FISSION FUNGI OR SCHIZOMYCETES.

First let us settle the question of what we mean by bacteria, as the terminology of this group of minute beings has become somewhat mixed and confused. The great discovery of Davaine, that the disease of cattle called anthrax was really

due to a rod-shaped organism, doubtless instigated the research which has now proved so many diseases to be due to the presence and growth of micro-organisms; to this special research the name of 'bacteriology' has been given. It was soon found that many of these minute organisms are not rod-shaped, hence many new terms came into use, such as 'micrococci,' 'vibrios,' 'leptothrix,' etc.; to obviate the inconvenience arising from the multiplication of names, Sédillot, in 1878, proposed to designate these organisms under the general term of 'microbes' (*μικρος*, little, *βιός*, life), which merely implied the existence of properties upon which everyone was agreed. This term was for some little time very well received, and is very well known to the public; yet it has one great disadvantage, which is, that it may equally well include the lower forms of animal life, such as the Gregarinidæ as well as those of the lower forms of vegetable life, such as the Algæ. By common consent we now take the term 'bacteriology' to mean that science which deals with the laws that govern that group of organisms which exists at the bottom of the scale of Nature, forming possibly the link which unites animal to vegetable life, those organisms being termed 'bacteria,' irrespective of their shape or size, which possess certain properties in common. They are everywhere distributed through Nature, in air, water, and in dust, being deposited on, and clinging to, the surfaces of every substance or material exposed.

In structure they are non-nucleated unicellular organisms, with few exceptions being destitute of chlorophyll, are all microscopic, some even approaching the limits of microscopic visibility; they consist of a sac, or structureless but sharply contoured membrane, composed of a gelatinous substance allied to cellulose—but which is not a true cellulose, nevertheless—enclosing a soft, semi-fluid, homogeneous or granular protoplasm, which is more or less prone to be stained with basic aniline dyes, like the chromoplasm in the nuclei of animal cells. Under the microscope they appear as pale,

translucent, highly refractile bodies, and, when existent, spore formation and motility can be observed, but little else, unless the bacteria are stained. Some authors have described a nucleus, and certain appearances have sometimes appeared to warrant this conclusion. At times, irregular, deeply-stained granules are observed within the protoplasm, resembling a chain of beads; these have been termed 'metachromic granules': sometimes rounded or oval unstained portions may be observed at the poles of the bacterial cell, called by the Germans 'polkörnchen'; these metachromic and polar granules, however, are not nuclei at all, as will be demonstrated later, nor are they spores, but are indications of a degenerative change in the protoplasm produced by a process called plasmolysis.

Very recently bacteria have been divided into a simple or lower group and a more developed or higher group. It is the former which chiefly concerns us.

The lower bacteria may be divided into three classes, according to the form they exhibit.

1. Of a globular, berry-like, or spherical shape; these are termed 'cocci.'
2. Of a straight rod-shape, with the length at least twice the breadth; these are termed 'bacilli.'
3. Of a curved or spiral form, often like a bent rod; these are called 'spirilla.'

These lower bacteria are unicellular masses of protoplasm surrounded by a cell wall; endogenous sporulation may occur, and they may be motile.

1. *Cocci.*—These are very small, on an average about 1 μ in size; they may propagate by division in any direction, hence, according to the peculiar methods adopted by individual species, we get from division in one axis only, cocci arranged like a chain (streptococci), or in pairs (diplococci); from division in two axes at right angles to each other, double

pairs (tetracocci), or the same in a double plane, packets of eight (sarcinæ); it may happen that the division is quite irregular, from which collections are formed resembling a bunch of grapes (staphylococci), or even larger masses called zooglœæ, which are surrounded and held together by a glutinous intercellular substance. Cocci are often spoken of as micrococci; they are not usually motile; two species of cocci possess flagella.

2. *Bacilli.*—These are straight, rod-like, cylindrical cells, most of them measuring less than 1 μ in breadth, though they vary considerably in length. The influenza bacillus is the smallest with which we are acquainted, measuring only ·5 μ in length by ·2 μ in breadth; the tubercle bacillus is the most slender compared to its length. Bacilli may or may not be motile, possess flagella or not; they reproduce themselves by binary division, and in many species spore formation may occur, the spores being either situated terminally or centrally, and may be of various shapes.

3. *Spirilla.*—These are also cylindrical cells, but instead of being straight, like bacilli, they possess a spiral, curved or wavy form, of which two types can be distinguished: (1) as a long, slender, wavy, or spiral thread, being non-septate, such as Obermeier's spirillum of relapsing fever; and (2) much shorter, of a curved or comma shape, such as Koch's spirillum of cholera—these latter have been also termed vibrios; an appearance resembling the true spirilla may sometimes be noticed when two vibrios are lying end to end with the concavities of their curves alternating. The bacteria of this class may or may not be motile; most of the motile spirilla possess flagella; like other schizomycetes, they multiply by fission, and in some species endogenous spores have been noticed.

The higher bacteria are much more highly developed than the lower, and consist of either branched or unbranched filaments, which in most cases are septate, being divided at intervals into straight or curved elements more or less

mutually dependent upon each other, and usually enclosed in a common sheath or cell wall; nevertheless they enjoy an independence of function, some of them, indeed, being solely concerned in reproduction by the formation of conidia. The higher bacteria are divided into groups—beggiatoa, thiothrix, leptothrix, and cladothrix—which possess various distinctive differences, but have no pathological importance; they are usually found in dirty water and stagnant ponds. The last group, that of streptothrix, possesses the highest development of them all, forming a link between the fission fungi or bacteria and the group nearest to them of true fungi, being endowed with properties of each; it has great pathological importance, for to this group belongs the actinomyces, or ray fungus, already mentioned. In man the ravages of this fungus were, until lately, attributed to cancer. Another species of streptothrix has been described by Flexner, as lately as June, 1897, under the name of *Streptothrix pseudo-tuberculosa*, the disease of the lungs produced by it being very similar to rapid phthisis.

Bacteria all reflect light very strongly; they also cause turbidity in any culture fluid in which they may be present—at least, if in any quantity; some have been said to contain chlorophyll, but the organisms that do so are not true schizomycetes, but belong to the lower algæ or schizophytæ. Many species are brilliantly coloured when growing in masses, though this is not common among the pathogenic bacteria, neither is it quite certain whether the pigment is outside or inside the protoplasm; in favour of the latter view a pigment named 'bacterio-purpurin' has been observed in the protoplasm of some species. These pigments are supposed to be lipochromes derived from animal fat, but not much is known about them; it is more than probable that the colours of the expectorations in phthisis are largely due to chromogenic bacteria.

The size of bacteria is usually measured by micro-millimetres; a micro-millimetre is equal to about $\frac{1}{25000}$ of an inch,

and is represented by the Greek letter μ. These extremely minute measurements have the same disadvantages in conveying little to the mind as have the measurements of the immense distances of the celestial bodies. It gives us some idea of the earth's distance from the sun to state that if we set off in a fast train, going sixty miles per hour, it would take us about 175 years to do the distance, consequently it would only be our great-grandchildren, when elderly, who would arrive. In like manner we may state that when a microbe measuring a micro-millimetre in length is magnified 2,200 times it looks about as big as the letter *i* in the print of this book; if an ordinary man were subjected to the same magnitude, he would be about four miles high; this may give some idea how excessively minute these organisms really are.

Bacteria reproduce themselves by fission, or transverse division, from which they derive their name of schizomycetes. Among the bacilli, or rod-like form, the division always takes place in a direction at right angles to the long axis, elongating as it commences to divide, becoming at a certain point more and more narrow until complete separation takes place, and the two halves resemble the original microbe and are free to undergo the same process of fission. Among the spherical bacteria, or cocci, in addition to fission at right angles to the long axis, segmentation may take place in two or three directions at right angles to each other in different planes; it has been already remarked that the cell wall consists of a glutinous substance like cellulose, and it is according to the peculiar agglutination of the divided cells that we find the different forms mentioned on p. 19.

The spore formation may either be in the form of (1) endogenous spores or of (2) arthrospores.

Endogenous spores have never yet been observed among cocci, but are very frequent among the bacilli and in some species of spirilla. The spore commences as a minute point in the protoplasm of the cell; it attains maturity in a few hours,

when it appears as a roundish, oval, or truncated rod-shaped, highly-refracting body, consisting of protoplasm and fat, enclosed in a tough capsule : they may occur in the centre of a bacterial cell, at one extremity or at both, are always shorter, but may be broader than the original bacterium ; often they resemble vacuoles. The vitality of the bacterial cell is consolidated into these spores, which, by means of the dense capsule, are capable of resisting to an exceptional degree the destructive action of heat, chemicals, or unfavourable surroundings, and on this account they also resist staining by ordinary methods. When placed in favourable conditions and supplied with fresh food, the spore breaks through its case and takes on the form of the original bacterium from which it sprung.

Arthrospores are certain bacteria, such as streptococci, which have taken on a resting or resistant state ; they swell up, the whole protoplasm acquiring the properties of a spore, but the cell wall does not appear to thicken, as it stains well with ordinary methods ; yet as they seem to have acquired greater powers of resistance and reproduction, they have been considered as spores.

Regarding the chemical constituents of bacteria, very little is known, and very much yet remains to be done on this point ; but it appears, from the labours already undertaken, that the chemical constituents of bacteria do not differ very much according to their species, but according to the conditions under which they have been cultivated. Cellulose and fatty matters have been isolated, also an albumin which contains salts of sodium, potassium, and magnesium, but contains little or no phosphorus, thereby differing in a marked degree from the nucleo-albumin of animal or of yeast cells.

We have now arrived at the end of the description of formed ferments ; there remains to pass in review their functions and biology—that is to say, their life-history.

To whichever of the three groups they may belong, some

of these formed ferments live, reproduce, and have their being *only* when provided with a good supply of fresh air or oxygen, from which peculiarity they were termed by Pasteur 'aerobics,' whilst others only thrive and carry out their functions when totally deprived of oxygen—these are termed 'anaerobics.' Others there are which belong to the first or aerobic class, yet possess the power or faculty of living a modified existence with little or no oxygen present; these are called 'facultative anaerobics.' Others, again, which belong properly to the second class, may under certain conditions and circumstances exercise growth and function in the presence of oxygen; these are termed 'facultative aerobics.'

The life-history of these formed ferments demands an inquiry into the effect produced upon them by outside agencies, such as (1) physical agents and (2) chemical agents.

1. The action of temperature upon these minute bodies is exceedingly important, because it is by means of this that we are enabled to separate one species of ferment from another, which would probably be indistinguishable from it were it not for this means. This is especially the case in dealing with yeasts. All formed ferments have a temperature which best suits the individual variety, a selected temperature, often called the optimum temperature; but besides this one there are two others equally important, viz., the maximum and minimum temperatures, beyond the limits of which growth does not take place and their functions cannot be exercised, though their vitality may not be destroyed, but only remain in abeyance. Spores resist a very considerable temperature, maintained during a length of time, but none, except the thermophile bacteria, which have no pathological importance, can survive a temperature of 57° C., if applied long enough. The resistance of these cells, on the contrary, to the prolonged application of extreme cold is most remarkable, for, if carefully and gradually restored to a favourable temperature, they will regain their activity. Temperatures as low as −200° C. have

failed to destroy them, and some yeasts will begin to show some function even at a temperature of 2° or 3° C.

Formed ferments, when cultivated above or below their optimum temperature, are apt to lose their individual peculiarities or their virulence. Yeasts only show peculiarities at certain temperatures, and it is almost entirely due to the experiments of Hansen of Copenhagen on the formation of films and spore formation by yeasts at varying temperatures that we are enabled to distinguish between certain varieties.

The effect of pressure, up to 400 atmospheres, maintained for several days, is not destructive to formed ferments, neither does it appear to alter the cells, for yeasts, after having been submitted to such a pressure, show no appreciable alteration of form, and behave exactly as if cultivated in the ordinary manner, if they are subsequently placed in a saccharine aerated wort. Yeasts do not exercise their functions under pressure, though they commence the moment the pressure is removed, a fact we make use of in storing the formed ferments for therapeutic purposes.

Many of the mucors grow best with little or no light. Direct sunlight is injurious, and in many cases destructive, to them, which may with equal propriety be said of bacteria, for when in a dry state anthrax and typhoid bacilli are totally deprived of vitality by an hour and a half's exposure to bright sunlight. Even the diffused light of the laboratory has to be guarded against on a fine day when dealing with culture experiments. The electric arc has a similar effect, though electricity itself has not much influence over formed ferments, unless very large sparks—10 or 12 inches—are passed through them when in a moistened state, which quite destroy them; so will a current from a battery of ten Bunsen elements. A small amount, on the contrary, acts as a tonic and favours fermentation. Latterly, numerous experiments have been made with the ultra-violet X-rays, upon bacteria chiefly, over which they appear to have a certain ill-defined inhibitory, or

possibly destructive, effect. I cannot say that the results are very conclusive, and they have certainly led to no therapeutic successes.

2. The action of chemical agents over ferments offers many points of interest. The effect of oxygen we have already noticed; hydrogen and nitrogen are indifferent gases to all ferments, having no action over them whatever; carbonic acid, nitrous oxide, and carburetted hydrogen are neutral to all except *Bacillus anthracis* and *Bacillus pyocyanicus*, over which carbonic acid exerts a marked influence under pressure, the former losing its power of sporulation, and the latter losing its entire vitality. The action of chloroform is to hinder or prevent the functions of an old yeast or an old bacterial culture, but when young and vigorous their action is merely retarded by chloroform. Quinine acts like strychnia, both having the effect of first stimulating and subsequently depressing the function of ferments. Morphia has a retarding action, and cocain a markedly inhibitory one over ferments, and in the case of yeasts, the latter often stops their action altogether. Hydrocyanic acid and salicylic acid also possess inhibitory powers over the function of formed ferments, the latter being frequently used by the Germans in exported beer to prevent further fermentation.

A slightly acid medium is an advantage to yeasts; but if the acidity is increased to a very small extent beyond a certain point, fermentation is checked and proceeds very slowly. A still greater acidity checks it altogether, though a little depends upon the particular acid used, tartaric and hydrochloric acids being much better borne than others. Small quantities of alkaline bases have no hindering effect upon the functions of yeasts, for we have often seen a perfect fermentation occur after the medium has been rendered alkaline by an excess of phosphate of soda. This has an important bearing upon the whole of our subject, for, as will be seen later on, yeasts will have to perform their functions in the alkaline

medium of the blood; ammonia and the alkaline carbonates do have a retarding effect, and may prevent fermentation altogether. Bacteria differ considerably from the other formed ferments, inasmuch as they prefer a slightly alkaline medium indeed, some of them, such as the cholera vibrio, will not grow in the presence of the smallest trace of free acid.

The chemical agents which are most destructive to the life and function of the ferment cells are the salts of the heavier metals, such as the perchlorides of mercury, platinum and gold, of which the former is infinitely the cheapest, and one of the most powerful, 1 part in 10,000 being more than the majority of ferments can stand without eventual destruction, although a very much stronger solution is generally used as a bactericide, such as 1 in 1,000 or 1 in 2,000.

Besides these inorganic substances, there are many organic that are exceedingly destructive to ferments, the best known of them probably being carbolic acid, which is exceedingly effectual against most microbes, but not all; many stearoptines, such as thymol, are exceedingly bactericide, so also is benzoic acid, which has the advantage of not being deleterious to animal life; the same may be said of formalin, which is a 40 per cent. solution of formic aldehyde gas in water: this, in the proportion of $1\frac{1}{2}$ to 1,000 of water, is only second in bactericidal power to corrosive sublimate.

From aldehydes we pass on to alcohol, which is a most powerful antiseptic, and the one that we use preferably for sterilizing our needles before use. We must not forget that there are some curious facts relating to the destructive action of the life products of bacteria upon the same species as produced them, as well as over some others; also, contrariwise, some bacteria seem by their presence to pave the way and prepare the ground for the reception of other kinds which, without the previous presence of the first, would have been unable to have effected a footing in that particular medium.

As examples, we may say that firstly all ferments are rendered inert or are destroyed by their own products and secretions; that the cholera vibrio renders the medium in which it grows totally unfit for the growth of any other kind of bacteria; and it is a curious fact that this same vibrio is prevented from developing in media to which the *Bacillus pyogenes fœtidus* has already had access. For an example to the contrary we may instance the tubercle bacillus, which undoubtedly prepares the way for the lodgment of many different species of exceedingly unwelcome guests. The knowledge of these peculiarities has a distinct bearing upon the treatment we advocate, for, as we shall see later, the soluble products of the yeast cells when *in vitro*, or within the blood, acquire the properties of an alexin, thereby transforming the toxins secreted by bacteria into antitoxins.

This will close all we feel it is necessary to say on the subject of formed ferments—necessary, that is, for the purpose of this book, though the subject is well worth some further study.

Enzymes.

We must now proceed to discuss the properties and peculiarities of enzymes, or soluble ferments, after which we shall sum up in the next chapter the part that ferments play in Nature by describing the nature and mode of their functions, which are known by the term 'fermentation.'

Enzymes possess no structure, neither have they any power of multiplication; they are soluble, and very difficult to isolate from the protoplasm of the cells of formed ferments in which they are normally found, as well as within all the secreting epithelial cells of the system. They possess a very similar power to that enjoyed by the formed ferments, whose functions they actually imitate, as has been conclusively proved as regards the intracellular enzyme of the yeast cell commencing the saccharine fermentation; so also do the

enzymes of other cells provoke chemical changes in other media, according to their special functions.

By means of the enzymes contained in the cells of the salivary glands, stomach, pancreas, liver, and intestinal glands, the albumins of the food (proteids) are converted first into albumoses, then into peptones, in which state they are soluble, non-coagulable, and dialysable—consequently easy of absorption into the system. Likewise starchy foods are altered into dextrine, dextrose, and lævulose, which will be further described in the chapter on diabetes; finally, fats are emulsified or saponified by the same means to render them fit for absorption by the lacteals.

It may not be wrong to say that all metabolisms and tissue changes that occur in the body are in reality local fermentations, provoked by enzymes contained in the protoplasm of all the various cells of which the system is composed, the products of these fermentations being the normal leucomaines, leucin, tyrosin, xanthine, etc. Recent researches (Luff, B. M. J., 1897) tend to show that diseases like gout are caused by the action of enzymes upon complicated nitrogenous media, causing first the formation of the quadriuret of soda, and then its reduction to uric acid, which is eliminated by the kidneys, but if in excess is deposited in the tissues.

CHAPTER II.

FERMENTATIONS.

We have said in the previous chapter that the term 'fermentation' is applied to the phenomena of function in ferments: it was formerly limited to those processes characterized by the formation and ebullition of gas, such as those of wine-making and of beer, hence the term (from *fervere*, to boil); but it has now a much wider signification, and is taken to mean any chemical change or metamorphosis set up in complex organic substances through the agency of a body derived from the animal or vegetable kingdom, by which they are reduced to simpler elements, the original organic substance acted upon being quite disproportionate in bulk to that of the agent. Every ferment has a predilection for a certain food, a certain temperature, and other conditions such as have been already mentioned; upon these conditions the result of the fermentation depends.

The fermentations caused by the first of those groups into which we divided the formed ferments need not detain us long, as they have very little bearing upon the main object of this work; suffice it to say that some of the mucors, or headed moulds, have the power of provoking alcoholic fermentation in a saccharine liquid, their cells budding like true yeasts whilst engaged in this work, though it is performed to a far less degree and far more slowly also than it is when true yeasts are the active agent; consequently their presence or

adventitious mixture with yeasts embarrasses the latter in their work, and tends to spoil the result of their action, a point which must be borne in mind when we come to deal with the selection and purification of yeasts and the preliminary sterilization of their fermentable media. Although the mucorineæ, or moulds, may usurp the functions of the saccharomycetes, or yeasts, even to the extent of imitating their peculiar modes of reproduction, yet the one can never remain permanently with the acquired functions of the other, as may be proved by returning the mould to its own proper medium, when it at once resumes its natural mode of growth : it is as well to remember this point, as it is equally true with respect to bacteria, so long considered polymorphic, giving such trouble to their investigators in their attempt to differentiate between them, that many were of opinion that one species could actually turn into another, though we know now that this is impossible : the laws of Darwin, equally applicable here as throughout the rest of Nature, forbid us the conclusion ; also we can satisfy ourselves by placing a doubtful organism under several known conditions of culture, when succeeding generations will quickly determine its place and true name.

The fermentation by yeasts is the best known of all the fermentations, both industrially from the mead of prehistoric times to the scientific brewings of the present day. More labour and research have been expended upon this, the alcoholic fermentation, than upon any other ; and upon the ascertained facts and peculiarities pertaining to it we base our own further researches, and deduce our theories concerning the more complex fermentations, including those of disease, to be described later on. Alcoholic fermentation, so easy to produce and study, is found to be a standard type of all other fermentations. It is the typical manifestation of the phenomena produced when a ferment, of whatever nature, is placed in presence of the medium and conditions of its predi-

lection; hence to describe this is to describe all, which, however they may differ in detail, never differ in the principal or main characteristics.

A saccharine substance, such as malted barley, is mashed in water in certain proportions, together with nitrogenous and mineral matters, which are already present when barley is used, but when other saccharine is used these require to be added, and the exact quantity of each determined by experiment, too great a quantity of either ingredient being a hindrance to the proper performance of the function. The wort having been duly made and sterilized from any foreign element, is then well aerated, the yeast added to it, and the whole maintained in a temperature of about 18° C. Under such favourable conditions the yeast cells acquire great vigour and enter into active proliferation, for which purpose they absorb a considerable amount of oxygen from the liquid, though they return it very speedily as carbonic acid, which can be seen rising in bubbles to the surface of the liquid. As yet fermentation has hardly begun, but as the oxygen disappears from the wort, cell proliferation diminishes and a new set of phenomena commences both by the original cells and their progeny, by the means of the invertin contained in them. The saccharine material, of whatever kind it may be, is reduced to invert sugar, and the very moment this process is completed the yeast cells proceed to still further split it up, storing and assimilating for their own sustenance and future use certain elements to form a reserve of glycogen or other carbo-hydrate in combination with the protoplasm of their cells. The remainder of the sugar, which is valueless to the yeast cell, is thrown out by it into the surrounding liquid; part can be seen as carbonic acid escaping from the liquid by violent ebullition, part remains within it as alcohol, glycerine, succinic acid, etc. This process goes on until one of three things happens: The carbonic acid may not be able to escape, and the pressure stops further fermentation, which can be

seen in a bottle of champagne or one of our cartouche tubes, to be afterwards described. The amount of alcohol poured into the liquid may be in so great quantity that the yeast cells can no longer act, for it is a law of Nature that all creatures lose their vitality when exposed to the toxic action of their own excretions. An example of this arrest of fermentation is seen in port wine, which contains a large amount of unfermented saccharine; when kept for years in either bottle or cask, the alcohol slowly evaporates through cork or wood, and is as gradually replaced by more alcohol from the remaining saccharine. By this extremely slow process the coarser alcohols are eliminated and the finer alcohols retained, together with subtle aldehydes and æthers which give the exquisite flavour and bouquet to old bottled wines. The third thing that may happen is the exhaustion of the saccharine in the medium, and when this occurs the yeast cells live for a time upon the reserve of glycogen that they have stored up within them, but eventually, unless they are provided with a fresh supply of saccharine, they languish and die.

The phenomena of fermentation vary with the temperature, amount of aeration, etc., so that it is quite possible to obtain a free cell proliferation, a free production of alcohol, or even the two combined; for instance, if a continual current of air is made to pass through a wort that has been impregnated with yeast, the cell proliferation is much greater than in a wort that is still. If, on the contrary, we desire an abundant production of alcohol as well as much cell proliferation, the current of air must be passed through the wort before the yeast is added, after which it is left until it is in full activity, when it is again submitted to aeration.

In order to obtain cells in a state of vigour, we must collect them at a time when the fermentation is in full activity, or at least we must not wait until the wort is exhausted of either its saccharine, albuminoid, or mineral

elements, for then the cells would be at the end of their vigour and probably about to degenerate. It is easy to conceive that yeast cells collected at a time when they are gorged with a reserve of glycogen, then duly oxygenated, and finally preserved in a latent state (by a process we shall describe in a subsequent chapter), possess a power of effecting a footing and maintaining a hold even in an unfavourable medium, and exercising their functions therein by means of the richness of the reserve food they have stored up : this is especially the case when, in addition to their own store, they have added to them such food as they require when under anaerobic conditions, and this is one of the most important points, demanding all our care and attention in the preparation of the material to be injected together with the yeast cells when used therapeutically. Our cells resemble the soldier who carries three days' rations on his own person, in addition to which there is the commissariat train, on which he can depend, as it is quite uncertain as to what food, if any, he may get in the country he is about to invade. For the invasion to be a success, absolute and extreme purity are essential conditions—purity of the yeast cell, purity of the aeration, and purity by sterilization of the added nutrient material.

We have seen that the saccharine elements have been split up by the action of the yeast cell during fermentation, but this is not all that goes on, for the same phenomenon occurs with the nitrogenous and mineral matters that are present in the wort, the cell extracting from them what it requires, and returning to the surrounding fluid the whole of the residue, which of course is variable with the composition of the wort, and also with the conditions under which the phenomena of fermentation took place. A slight difference of temperature is often quite sufficient to alter both the nature and relations in weight of the products of fermentation, yet the most considerable changes, when proper precautions

are neglected, are due to impurities, either in the yeast itself, in the air, or in the wort.

We shall have occasion later on to say more upon the subject of wild or foreign ferments, a subject which, as Dr. de Backer says, has been not perhaps the base, but the accidental cause, of all our researches.

Besides alcohol and carbonic acid as products of fermentation, formerly believed to have been the only ones, we have mentioned succinic acid, discovered by Schmidt of Dorpat, and glycerine, first noticed by a German apothecary, but chiefly made known by Pasteur. It may reasonably be asked, Where do these bodies come from? Let us turn to the formula promulgated by Gay Lussac, who was quite unaware of the presence of these two bodies. Cane sugar, $C_{12}H_{22}O_{11}$, with one molecule of water, H_2O, is changed by invertin into grape sugar, $C_{12}H_{24}O_{12}$, which is still further split up by the yeast cell into $4C_2H_6O$ (alcohol) and $4CO_2$ (carbonic acid).

Now, 1,000 grammes of saccharose after fermentation yields rather more than 1,036 grammes of products in the following proportions :

Alcohol	506·15
Carbonic acid	492·95
Glycerine	28·30
Succinic acid	4·52
Other bodies	4·11
	1,036·03

The other bodies consist of higher alcohols, glycols, æthers, acetic acid and nitrogenous matters. Now, glycerine being a compound of carbon, hydrogen and oxygen ($C_3H_8O_3$), it may possibly be produced from compounds of the same elements, such as sugars ; but if so, it is a most extraordinary reaction, utterly beyond all laboratory skill, hence we are forced back to the opinion that, after all, the chemical equation of Gay Lussac is perfectly correct, and that the true source of the glycerine must be found elsewhere, and the solution may be found in

the action of metabolism by the protoplasm of the yeast cells, which throw it out or exude it as an excretion. Udransky has shown that glycerine is formed just at the time when the wort begins to be exhausted and the yeast cells inclined to enter into degeneration. It is therefore most probable that the glycerine originates from the decomposition of the fatty matters which the cells always contain within their protoplasm, and which can be separated without much difficulty by macerating the cells in a mixture of æther and alcohol for forty-eight hours. The succinic acid ($C_4H_4O_5$) is probably formed synthetically by the oxidation of butyric acid ($C_4H_8O_2$) or the reduction of malic or tartaric ($C_4H_4O_6$) acids, which are nearly always present, in combination, in fermentable fluids. The remaining elements—higher alcohols, etc.—as enumerated above, are in all probability due to the phenomena of the process of degeneration in the yeast cells, and the presence of leucin and tyrosin amongst the nitrogenous matters reminds us very forcibly of the waste products of the human body : it is only in large quantities that these products of metabolism are at all important, and as we are most careful to catch our yeasts at their full vigour, we practically prevent them from being excreted, and in any case their extremely small quantity would have no deleterious effect.

We may form some opinion upon the enormous vital energy of these microscopic bodies when we come to consider that quite a small quantity of them, a mere pinch, in fact, is sufficient to produce the complete metamorphosis of a kilogramme of sugar, to acquire chemically a quantity of water weighing 55 grammes, during the inversion of the sugar into glucose ; to split this up, to utilize the energy and caloric thus set free in organizing and manufacturing the various elements necessary to the development of the young cells, which have by this time amounted to about 15 grammes (reckoned in the dry state). A wonderful power, truly ; let us, then, use this power in overcoming and conquering disease.

Fermentations by bacteria differ but in degree. We have already observed that these microbes increase and multiply by division of their cells, but we must here point out that this process cannot take place unless the bacteria are placed in a medium of growth suitable to each individual species—that is to say, provided with proper food and in favourable surroundings; these being provided, cell multiplication takes place with enormous rapidity, much faster than the yeast cells can accomplish by gemmation. But although the actual mode and rapidity may differ, the life-history, nevertheless, is very much the same in both. The bacterial cell absorbs the food into its interior, splits it up, retaining as much as it needs, and ejects the remainder in the form of simpler and more stable compounds; this process is nothing more nor less than fermentation, which may be fulminating in its manifestation as plague, or it may be hardly perceptible, as in the gradual falling away of decaying plants or animals. Indeed, this ultimate reduction of organic substances into simple elements is the great rôle in Nature that bacteria are designed to play, and it cannot be denied that this is a most beneficent ordination; it is only when the pathogenic bacteria attempt to exceed their rôle by reducing us to simple elements before we have accomplished our life's work, that it is necessary and imperative to keep them within due bounds or destroy them. Fortunately, most bacteria are innocuous to living plants and animals, and carry on their appointed task of breaking down and resolving dead organic matter by a process of fermentation called putrefaction; so many kinds of bacteria, so many different kinds of fermentation, all, however, being on the same plan, which is the abstraction of a small portion of the organic chemical constituents, for their own nutrition, from the dead substances with which they come in contact, whereby the chemical equilibrium is destroyed and the residue recombines into simple inorganic elements. Before this final stage is reached these products, or residues, may remain for some

time; they are frequently poisonous, sometimes intensely so, especially when in the form of ptomaines or cadaveric alkaloids. Fortunately, it usually happens that in this class of fermentation, or putrefaction, the bacteria also excrete gaseous products possessed of a loathsome and disgusting smell, which gives us good warning to beware. In addition to these bacilli of putrefaction, or saprophytes as they are termed, we find others that live either upon the surface or within the interior of animal or vegetable organisms; they are parasites, and may be of a distinct advantage to their host, as in the case of those bacteria which are found in the tubercles on the roots of leguminous plants as well as in the surrounding soil, for these have the power of oxidizing ammonia. and so forming nitrates and nitrites from the ammonia of the soil and the air, thus rendering it into a state in which it can be assimilated by growing plants. This process, called nitrification, also occurs in well-water that has become contaminated with sewage; this kind of bacteria may also render service to the animal host—a case in point is the new-born child, who would be perfectly incapable of digesting the first milk of the mother, unless it were for the presence of the *Bacillus coli communis.* This same bacillus normally plays a friendly part throughout our lives, for there are certain substances which are taken into our alimentary tracts, but which no human ferment has the power of dissolving or rendering assimilable—such is the case with cellulose, yet it certainly does get converted into glucose and is absorbed, this conversion taking place in the intestine by this particular bacillus.

On the other hand, many other bacterial parasites are far from being an advantage to their host, but are harmful, noxious, and even deadly. It is to these that we shall give the greater share of our attention, inasmuch as it is to show the life-history of these within the human body that this work has been undertaken, in view of exposing a new means of controlling or aborting their fermentations — in

other words, of curing the diseases to which they give rise.

It is exceedingly probable that all parasitic bacteria were originally simple, harmless saprophytes, but which by a perversion of instinct have became facultative, and finally obligatory parasites. An example of this perversion may be seen in dipterous insects, such as mosquitoes, gnats and horseflies, whose natural food is the juice of reeds and succulent plants, but which have come to look upon man and other animals as ambulant plants. No very clear line can be drawn between parasites and saprophytes, for we may see some species of virulent parasitic bacteria, when under attenuation culture, taking on a saprophytic action ; or we may see the reverse, such as in cases in which the bacillus of tetanus or of malignant œdema has gained access to the blood current of the economy—bacilli whose natural habitat is the soil of stables or gardens respectively.

What we have already said about yeasts we must also repeat here, and with greater stress, concerning bacteria, which is the importance of the media and other conditions of culture best suited to the development of the various individual species. With yeasts these conditions have been thoroughly well ascertained ; we know the food, the temperature, the amount and best period of aeration, with other conditions requisite for each variety, but what do we know about the food of choice or conditions of predilection preferred by the many different bacteria which invade the body, and against which we have to contend ? Next to nothing ! And what do we know of the chemical, or physiological, or chemico-physiological condition of the contents of our own bodies, which are sometimes in a state of receptivity for bacterial fermentation, and at others in a state of resistance ? Very little ! Our bodies may be compared to a wine or beer cask, represented by the skin and mucous membranes, full of a wort whose composition is more or less generally known, but which

is constantly varying from hour to hour; this is represented by the blood, lymph, and softer tissues. If a wort be previously sterilized, and the cask also, which is then hermetically sealed, no fermentation can ever take place, because no ferment can ever get in. So also may the wort in our bodies be hermetically sealed against invasion by the continued action of the nervous system which governs our organism, and if this be sound and vigorous, a potential sterilization of our blood and tissues is maintained. As the cask is assailed by myriads of ferments from without, so are our bodies by exposure and by ingested food, but no harm can happen to the economy so long as the balance of nerve control is maintained; let, however, some little accident cause a minute puncture in the cask, or let the nerves relax their control over the system: ferments enter, infection has occurred, and fermentation will commence. Not at once, however; sometimes, indeed frequently, the nerve control is regained, and our resisting forces, partly described already, are called up, come into action, destroy the bacteria, and so save the system; in this we have the advantage over the wort in the cask.

Let us strain the analogy another link. The formed ferments having effected an entry, there exists a period of tranquillity in the medium, be it blood or wort: this quiescence is merely relative, and, although nothing can be detected by the senses, yet cell proliferation is actually going on, and this constitutes the period of incubation, lasting a varying time according to the nature of the infection—that is to say, as to what particular yeast has effected an entrance into the cask, or what specific bacterium has invaded the blood. Knowledge of the interval which elapses between the time of infection and film formation in one case, of sickening in the other, is of very great importance in enabling us to decide with what particular ferment we have to deal. The first manifestation of fermentation in yeasts is seen by the formation of films, and in disease by the phenomena called sicken-

ing ; from this time onwards the fermentation, or fever, is in full swing, accompanied by rise of temperature. Each fermentation or disease has its own peculiarities : the Germans use ice very largely to control the temperature in their fermentations ; physicians also use it largely to reduce temperature in zymotic diseases. Not only are peculiarities of temperature noted in fermentations, but peculiarities many and various, called phenomena when speaking of industrial fermentations, but termed symptoms in those pathological, *i.e.*, disease. The ebullition of fermentation, or fever, may attain such proportions that the cask may burst ; we are told not to put new wine into old bottles, or the patient may die from the intensity ; otherwise the fermentation, or fever, subsides, convalescence ensues, a condition in which an addition of the same ferment will produce no further action : this forms one kind of immunity. As the animal had an advantage over the cask by means of its power of being sometimes able by its vitality to destroy the ferment at the commencement, so at the close it is at a disadvantage. For although the cask may be strained, and rendered rather leaky, it is not much the worse ; but the animal system may be, and usually is, definitely poisoned by the products of excretion of the bacteria, called 'toxins,' which have the power of dissolving the tissues by a species of digestive action, so that the patient is a long time in recovering, it may be years, or he may never recover, but die of secondary poisoning. This is particularly the case after diphtheria, and in a less degree after influenza, in which, if death does not actually occur, a long, slow, extraordinary convalescence commences, in which the weakness and general prostration is out of all proportion to the length or severity of the original attack. There can be little doubt that this tremendous depression, insomnia, and feebleness of the heart's action, is entirely due to the effects of the toxalbumoses produced by the fermentation of the influenza bacillus.

Although immunity is attained, which in some cases may

last the whole of life, as generally in small-pox, or for only a very short time, as in influenza, the system is immune to this particular ferment only ; indeed, it happens at times that the result of one kind of fermentation may actually predispose to the action of another, as is seen in the strange relationship which exists between scarlet fever and diphtheria ; a somewhat similar instance is the preparation for an acetous fermentation by one that is alcoholic, the former not being possible until the latter has preceded it. Besides this preparation of a medium by one kind of ferment for the subsequent development of another, there remains yet another phenomenon to be considered, which is that of *bacterial concurrence*, by which is meant that one species of bacterium cannot under certain conditions exercise its full functions unless in the presence of a certain other kind. Roger has shown that the rabbit is ordinarily refractory to symptomatic anthrax ; but if the *Bacillus prodigiosus*, or even its soluble products, be injected at the same time as that of anthrax, the rabbit will take this disease, from which it will die in forty-eight hours. The odd part of this is that the *Bacillus prodigiosus*, and its products likewise, are perfectly harmless to the rabbit when used alone. This principle of concurrence has been made use of by Dr. Coley in the preparation of his serum for the cure of malignant disease, which he makes by mingling the life-products or toxins of the streptococcus of erysipelas with those of the *Bacillus prodigiosus* just mentioned. Dr. Bokenham has also suggested an antidiphtheritic serum composed of the usual antitoxin with equal parts of the toxins of the erysipelas streptococcus.

Finally, we have to consider *microbic associations*, in which bacteria of various sorts live together in symbiosis and harmony, each playing its own particular part distinct from the others ; an example may be seen in Nature in the fermentation of kephir (the national drink of the Caucasus), wherein an alcoholic ferment and a lactic ferment exist side by side.

Perhaps a more familiar example may be found in ginger-beer, the national drink of the English schoolboy; here we find an ordinary yeast existing in close symbiosis with a bacterium, their united effect being the production of a little alcohol with a large amount of lactic and carbonic acids. As an example in disease, I would direct the reader's attention to the sputa of patients in an advanced state of phthisis, in which we find not only the bacillus of tubercle, but pneumococci and other diplococci, also *Staphylococcus pyogenes albus* and others, streptococci, tetracocci, *Bacillus pyogenes fœtidus*, *fluorescens*, *putridus*, *pyocyanicus*, and others; any or either of these may be present with any other, and I have seen some cases in which every one has been present: it is the mixture of these various toxins getting into the blood and digesting the tissues that has hitherto rendered the cure of phthisis so hopeless after the first stage is past.

Before proceeding to the study of the chemical or chemico-biological changes caused by the bacterial fermentations already described, it would be well to take a cursory glance at some others. The transformation of ammonia by oxidation into nitrates, etc., has been shown to be due to the action of bacteria, and closely allied to this fermentation by oxidation is the industrial manufacture of vinegar, in which alcohol is oxidized by the *Bacillus aceti* into acetic acid, two atoms of the hydrogen of the alcohol being replaced by one atom of oxygen, thus: $C_2H_6O = C_2H_4O_2$, or, more correctly, CH_3,CH_2,OH (alcohol) $= CH_3,CO,OH$ (acetic acid). The opposite to this is seen in fermentation by hydration, which is seen in the conversion of urea into ammonium carbonate by the acquisition of two molecules of water, thus: $CO(NH_4)_2$ (urea) $+ 2H_2O$ (water) $= CO(NH_4O)_2$ (ammonium carbonate); also, in lactic fermentation we find hydration in which one molecule of water is acquired, thus: $C_{12}H_{22}O_{11}$ (milk-sugar) $+ H_2O$ (water) $= 2C_6H_{12}O_6$ (dextrose), this hydration being further altered

by a simple decomposition, by which the $2C_6H_{12}O_6$ (dextrose) becomes $4C_3H_6O_3$ (lactic acid).

There still remains one more fermentation to be noticed, which is that of reduction, wherein the carbo-hydrates and fatty acids undergo a change, part of the carbon being oxidized and given off as carbonic acid, part of the hydrogen being given off in a free state, and part as water. These fermentations may be seen in the fermentations of cheese, the turning of butter, the butyric fermentation of milk, etc. A somewhat similar process goes on in the body by the enzymes contained in the protoplasm of certain cells.

The study of these various bacterial fermentations, from an industrial point of view, has been largely undertaken on the Continent, and is also gaining ground in America. The dairy-farmers there are enabled to produce with great uniformity a class of butter possessing the choicest flavour, consequently fetching the highest price ; and little Denmark, from being one of the most impoverished States in Europe only a very few years ago, is to-day one of the most prosperous, solely owing to the enterprise of her dairy-farmers and agriculturists, who study their business from a scientific point of view ; therefore their products find a ready sale in other countries, especially in England, whose farmers are quite content to jog on in the same way that contented their forefathers, and who do not care to interest themselves in new-fangled notions. Hence we hear a good deal about agricultural depression.

The products of bacterial fermentation are so important that they deserve more than a passing word. Yet the subject is one beset with difficulties, inasmuch as the composition of the media in which the pathogenic bacteria exert their functions is often so complex that we can say very little about the formation of the products, how much is due to the splitting up of the constituents of the medium, and how much to metabolism of the protoplasm of the bacterial cell. Analogy may

be drawn from the fermentations of yeasts, inasmuch as we know that the formation of alcohol beyond a certain point arrests the action of yeast cells, hence alcohol may very justly be termed the toxin of yeast. We have already mentioned that law of Nature by which all beings are destroyed when exposed to their own excretions, and this law is very rigorously applied to bacteria, for although their products or toxins are exceedingly deadly to creatures of a higher type, they are just as deadly poisonous to the very creatures which gave them origin. Let us, then, see as far as we can what are the products of the life-history of bacteria as revealed by experiment.

Given the special bacterium, the special composition of the medium, with the special conditions experiment has proved to be the most suitable for it, it should not be difficult to ascertain the results, and this can fairly well be done by experiments *in vitro*. We need not enter into the question of the products of bacterial fermentation that are found useful in industrial occupations, as they have no bearing upon the object of this work. There remain, then, the products of pathological fermentations to be considered, wherein the blood and tissues of man and other animals are the media, and their bodies the containing vessels. The signs or manifestation that pathogenic bacteria have successfully invaded the system happen so long after the actual infection, that the blood is by that time considerably altered from the condition which obtained at that particular time, the long interval rendering it almost impossible for us to ascertain what was the then actual chemical or biological condition, especially in regard to that of the leucocytes ; consequently we have rather to work backwards, as it were, and find out what are the general conditions that confer resistance in the healthy body, and what deviations from them permit the invasion by ferments. These points will be discussed in the next chapter, under the head of Immunity.

The phenomena of bacterial fermentation commence, just as in the fermentation of yeasts, with activity of the soluble ferments, or enzymes, contained within them; these enzymes are themselves highly poisonous to the animal economy; a common term for them is the intracellular poison. Most bacteria absorb proteid substances within their protoplasm when they become introduced to the enzymes, which immediately exercise their functions upon them and split them up, the cell retaining within itself the constituents necessary for its growth and multiplication, the residue being excreted as substances called albumoses, which have acquired, by the process to which they have been subjected in the bacterial protoplasm, a toxicity more or less virulent: these albumoses are also known as toxalbumins, or, more correctly, toxalbumoses. In some bacteria it appears that this intracellular poison is more diffusible than in other species; hence some escapes from the cell at the time of the excretion of the toxalbumoses, and is diffused into the surrounding medium, which explains how it is that bacteria, which are confined locally to certain regions of the body, beyond which they do not travel, such as those of cholera and diphtheria, are teletyptic in their action, being able to produce toxic digestion of tissues in regions remote from their personality. We are quite unaware of the nature of these enzymes or intracellular poisons, nor do we know whether more than one kind of enzyme, possessing different properties, may be enclosed in a single bacterial cell; this may be the case, for it is certain that in the case of diphtheria, for instance, there are formed two different kinds of toxalbumoses; these substances, after quitting the bacterial cell, become altered into toxipeptones, and in some cases, as in diphtheria again, to organic bases and acids, either by the further action of the diffused enzyme, or by protoplasmic action of the natural cells of the body wherein they suffer; probably the latter is correct, for it is certain that it is the toxalbumoses

which cause the after-paralysis in diphtheria, and not the organic acid, which, with very good reason, may be regarded as an alexin.

Not only are toxalbumoses, which are also called 'extra-cellular poisons,' from either being formed outside the bacterial cell, or at least ejected from it, formed by bacterial fermentation, but also other bodies resembling the vegetable alkaloids; they are very akin to the leucomaines or alkaloids normally formed in the body from the metabolism of tissues. The alkaloids formed by bacterial metabolic action are termed ptomaines, and are no doubt normally formed from the food in the intestines by the bacteria which are always present there; but, as a general rule, their poisonous properties are immediately neutralized by the bile; when from any cause this does not happen, a kind of auto-intoxication results, from the absorption and subsequent storage of these un-neutralized ptomaines within the system, which becomes considerably deranged thereby. When ptomaines which are formed outside the body are accidentally ingested with food, they are absorbed in the stomach, to which the bile has no access, with the result that the whole system is speedily poisoned, only too often ending in death. An example in point is the sad, and at first mysterious, death of a promising young officer of Engineers at Chatham a very few years ago, which was proved to have been due to the eating of a tinned sardine. A few months afterwards an instance of ptomaine-poisoning from the same cause came under the notice of the writer; out of a family of seven people, six were very seriously ill, and one of them very nearly died; copious vomiting, freely encouraged, got rid of most of the ptomaines; any that remained must have passed the pylorus, and so come under the destructive power of the bile. We have more chance of saving the patient when sardines are the offenders, because the poison is often surrounded by a coating of oil, which is not digested in the stomach.

Ptomaines and other cadaveric alkaloids are the products of saprophyte bacteria by the putrefactive fermentation of dead animal and vegetable tissues (see p. 40); most of them are poisonous, those derived from fish being so particularly. Many of them may be produced by synthesis, and these possess all the specific actions upon the living animal, just in the same manner as those alkaloids produced by decomposition. Under the name of ptomaines a large number of cadaveric alkaloids are included, which differ from each other, yet all possess certain characteristics in common; they consist of a nitrogenous base having an alkaline reaction, are generally crystalline, colourless, insoluble in water, but soluble in alcohol and chloroform, bear a close analogy to the vegetable alkaloids, are pungent and acrid to the taste; they combine with acids to form salts, which differ from the alkaloids themselves, inasmuch as they are soluble in water, less so in alcohol, and completely insoluble in chloroform; their bases are precipitated from their solutions by alkalies.

We need not concern ourselves further with these bodies, for what we have said is quite sufficient for the scope of this work; their properties and peculiarities may be studied in books on bacteriology. The diffusible enzymes and toxalbumoses are of great importance to us in our present quest, for it is upon the knowledge of these that the modern treatment by serumtherapy has been founded, and our still later treatment by pure ferments fixed on a sound scientific basis.

As yet our knowledge concerning these enzymes, intracellular toxins, or toxin-producing ferments, is all too limited; they have not yet been isolated in a pure condition; the very name 'toxin' has been exceedingly loosely applied to any substance either contained in the protoplasm of the bacterial cell, secreted or excreted by it, as well as to the results produced by their action either upon the media of their culture *in vitro* or within the living body by digestive action

on the tissues. Their absolute chemical natures are unknown, and probably differ considerably, according to the media in which they have been elaborated. The toxalbumoses, however, may be effectually separated by filtration through porcelain, which retains the bacterial cells, but allows the soluble products to pass through; the filtrate is then evaporated down to a third of its bulk *in vacuo*, at a temperature under 30° C., and precipitated by the addition of absolute alcohol; the precipitate is dissolved in sterilized water, and again precipitated, this process being repeated some half-dozen times. The final product is a snow-white mass, containing the properties of the original fluid, as regards its toxic effect, when injected into the animal economy.

It will bear repetition to say that all creatures languish and die when shut up with their own excretions or those of their own kind, of which an instance is afforded by the history of the Black Hole of Calcutta, in which 146 were incarcerated on June 20, 1756. The room measured no more than 20 feet square, and was provided but with two small windows, consequently the morning of the 21st found only 23 people alive; the remainder had died chiefly from the effect of the carbonic acid given off from the lungs and the skin of the prisoners, the time being too short for the other excreta to be reckoned as factors.

As with the highest creatures, so with the lowest, the bacteria; not only is this the case in respect to themselves, but it is still further true that their excreta render a medium unfit for the growth and development of a succeeding generation; this has been conclusively proved by Chantemesse and Widal, who from the surface of a gelatine culture of the typhoid bacillus scraped away all the products, and then impregnated the gelatine medium afresh with a new culture of the typhoid bacillus; the culture was sterile. Now, the toxalbumoses are the soluble products or excretion of bacteria, which, when they amount to a certain percentage within the

system, render it unfit for their own life or for those of their species, hence they languish, grow feeble, and are then dealt with by the natural defensive forces of the body; by this means recovery takes place, unless the system is so poisoned by the toxalbumoses as to be incapable of carrying on its function, hence systemic death ensues. These processes of bacterial attack and normal resistance by cells are exceedingly complex, and will be fully entered into in the next chapter.

CHAPTER III.

IMMUNITY.

The natural resistance to, or immunity against, any particular microbe varies very much, both as to the different species of animals and to different varieties of the same species.

Certain animals are immune against certain diseases, which immunity is hereditary, having been acquired from ancestors by a process of survival of the fittest to withstand the invasion of these diseases; this immunity, which may seemingly be complete, exists so long as the conditions obtain under which it was originally acquired, and is complete to that particular disease alone; for no immunity is so complete that there exists any animal which is immune against all invasion. Thus, horses, which are naturally immune against diphtheria, are very susceptible to glanders, against which other animals, such as rats, are immune; negroes are immune against yellow fever, which is so fatal to the white man, whilst many diseases which are trivial in the latter may have a very fatal effect upon the former. This high degree of immunity is, however, not absolute, for, as before stated, this only lasts so long as the conditions are maintained, at least, within certain limits. Thus, fowls are naturally highly immune against the invasion of tetanus, withstanding even large doses of the poison administered hypodermically, yet a dose *can* be given in this fashion which is too great for the creature's resistance, and it will die in tetanic spasms. In this experiment the immunity

has been overcome by the condition of quantity being altered, a larger quantity of poison having been used than any fowl could possibly acquire by its own initiative. As an instance of changed surroundings, examples may be found among the cold-blooded animals, such as frogs, which are naturally immune against tubercle and anthrax, yet lose this immunity, and may be invaded by these diseases, should their natural conditions of temperature be altered, and the animals maintained in a constant and warm-blooded temperature of 37° C.

Immunity may be of a less high degree than the foregoing, in which case an animal is said to be refractory to a disease. A less degree than this constitutes partial immunity, which, though considerable, may be only temporary, being apt to be suddenly lowered by various causes. Medical men and nurses, though being constantly brought into contact with zymotic diseases, enjoy a notable immunity against them, partly owing to their naturally healthy lives, partly owing to the steadiness of their nervous systems, acquired by the idea of any danger to themselves never even occurring to their minds; yet this immunity may be entirely lost should the subjects be exposed to infection when exhausted by long watching, fatigue, want of food, or all causes combined.

Contrary to the opinion generally held, that mothers and nurses are prone to be infected with diphtheria from their charges, I have never known this occur unless from the weakening of the nerve control from one or more of the above-mentioned causes. Partial immunity, which is our normal condition, slides in a descending scale until it reaches a point where there is not only no immunity at all, but a slight degree of an opposite condition, which is susceptibility or proneness to disease. Susceptibility exhibits the same peculiarities in many ways as does immunity in respect to the different species and varieties of those species. It may be

extreme, such as that of guinea-pigs to tubercle ; temporary or partial, until it meets a common neutral point with immunity.

Both immunity and susceptibility depend upon several factors, such as the age of the recipient, the condition of the nerve control of the system, the particular mode by which the microbe or its toxins attempt the invasion, and, finally, upon the condition of activity or virulence possessed by the particular bacteria at the time of their attack upon the economy. Either of them may be acquired or experimentally produced.

Immunity may be acquired completely against some diseases by a previous attack of those same diseases—smallpox, for instance ; or less completely, as after typhoid fever, still less so after scarlet fever, even less after measles, until we come to influenza, after which recurrent attacks are common ; we then arrive at an ascending scale with bronchitis and facial erysipelas, wherein one attack seems to render the system susceptible to succeeding ones. We have already called attention to the cellular struggle against the toxalbumoses during the time that the bacteria which gave them origin are dying from their presence. This struggle causes the natural cells of the body to secrete matters called alexins, which come to help the system and destroy the action of the toxins. The cells of the body, having once acquired the knowledge of how to do this, are able in a more or less persistent manner to retain the faculty of secreting these alexins, or products of resistance, which put the system, during the time the power lasts, in a state of resistance to a fresh attack of the same complaint—that is to say, immune against it. Immunity may be partially acquired by other factors, such as age, change of climate, etc.

Experimental immunity may be either direct (preventive) or indirect (curative). The former will first be noticed. Reference has been made to the similarity which exists

between the animal and vegetable alkaloids, and that many of the laws which apply to the latter are also applicable to the former. In early historical times it was known that the human body could be protected against the virulence of poisons by repeated minute or attenuated doses of those poisons. Mithridates, who died in the year 64 B.C., is said to have rendered himself so immune against all the then known poisons that his enemies might have used against him, that he himself, with all his skill and knowledge, was unable to deal himself death by poison when he wished to escape an approaching captivity.

This very same principle, two thousand years later, has once again been made use of in order to protect life, for we establish an immunity against a certain disease by injecting pathogenic microbes into the animal system, either in an exceedingly minute (sublethal) dose, or in which the virulence has been attenuated either by culture or by passage through other animals. Even this method has been considerably improved upon, and we have gone a step beyond. It was found that injection of the toxins produced by pathogenic bacteria in attenuated doses, repeated at suitable intervals, with a gradual increase of dose or of virulence, induced a high degree of immunity which is direct or preventive, thereby conferring immunity for a longer or shorter time, according to the particular bacterium and the particular mode of procedure. Haffkine's vaccine against cholera is a direct or preventive immunity, and is produced by a modification of the above process. It is not known exactly how long the immunity conferred by this vaccine may last, though it is certainly long enough to outlast the duration of an ordinary epidemic. These direct, preventive, or active immunities, as they have been called, are protective *only*, and are in no sense curative. The various means of producing attenuation of the bacterial virus more concerns bacteriology proper, and are but superficially noted here in respect to the amount of bearing they

have upon our argument ; so we now pass on to indirect or curative immunity.

In the course of various experiments it was discovered that the blood serum of animals possesses very decided and powerful bactericidal properties. The serum of rats is able to utterly destroy the vitality of the anthrax bacillus ; hence the experiment was made of injecting this serum into an animal susceptible to anthrax, either together with or subsequently to a lethal dose of the living anthrax bacilli, in order to ascertain whether it would have the power of arresting the disease. The experiment was successful, yet further experiment showed that the serum itself is, with some species of bacteria, only destructive to the vitality of their cells, not to the action of their toxins, and *vice versâ ;* this may be seen in experiments with Löffler's bacillus, which is not killed by a serum that is destructive to its toxins, and will even grow in it. It was next sought to ascertain if the serum of animals naturally immune against a disease could have its germicidal properties increased by a process of direct immunity. The result has been success beyond expectation, and to this we owe the antitoxic treatment of disease (indirect immunity).

The best-known and most extensively used of these antitoxins is that of diphtheria, and, as this is the most familiar, we will take the preparation of this as an illustration of the process usually adopted. A healthy horse, an animal naturally immune to diphtheria, and, from its size, capable of yielding a large quantity of serum without injury to its health and strength, is injected with a small dose (10 c.c.) of the toxins from a pure culture of the *Bacillus diphtheriæ*, from which the bacilli themselves have been eliminated by filtration through a Chamberland filter. A trivial swelling is produced, which soon subsides, and no fever is produced. As soon as the swelling disappears, a fresh injection is practised, and repeated two or three times a week, the dose being gradually increased according to the effects on the horse, which should be a

localized inflammatory swelling, with no effect upon the general health of the animal. After two or three months the injections, which have hitherto been practised subcutaneously, are now administered into the jugular vein, the dose being still further increased. The whole preparation takes about eight or ten months; though the process has been greatly shortened latterly by Cartwright Wood, who uses two toxins of different strengths. When the animal has been duly prepared, a quantity of blood is taken, with aseptic precautions, from the jugular vein, and the serum allowed to separate; a very small addition of carbolic acid is made, and it is then stored in tubes for future use.

The serum is standardized by testing a given quantity against a certain quantity of toxin whose virulence is known. The least quantity of toxin that will kill an animal is called the 'lethal' dose for that animal, and the quantity of toxin taken in standardizing is usually ten times this lethal dose. Various standards have been used, but the one devised by Roux is founded on the plainest principle; his standard represents the animal weight protected by 1 c.c. of serum against the lethal dose. For instance, if a guinea-pig weighing 500 grammes be protected by ·01 c.c. of a serum, then 1 c.c. of such serum will protect an animal weighing 50 kilogrammes—that is, equal to 50,000 grammes of guinea-pig.

Now, the object of the treatment by antitoxin is to introduce within the system of those suffering under a bacillary fermentation the same kind of complex substances, produced by such a fermentation, which are present in the blood during convalescence, and which neutralize the toxic action of the albumoses. Antitoxin is formed, in disease, by substances called 'alexins,' which are formed or secreted by the leucocytes of the blood and the lymph, from connective-tissue cells and others; from an animal naturally immune against a disease, these alexins are produced easily and in large quantities, without any strain or drain on its constitution, which

happens always when produced by susceptible animals. These alexins, dissolved in the blood serum, constitute the antitoxin which, injected into another animal, acts as a relieving army to a besieged force, the relievers being themselves completely armoured against the weapons of the besiegers. Let us carry the simile a step further, and it will be seen that the earlier the siege can be raised, the better state will the besieged be in; if delayed too long, most of the defenders of the fortress may be dead, or so weakened by the struggle as to be only capable of dragging on a miserable existence thereafter, the very fortress they gave their utmost to defend being little more than a heap of ruins. So with the body and its defenders; hence the antitoxin treatment must be begun as soon as the diagnosis is thoroughly established, in order to gain the advantages of the treatment; by so doing, the auxiliary alexins destroy the toxalbumoses as soon as formed, consequently but little demand is made upon the cells of the invaded system to form alexins of their own. I cannot tell if the cells of a system which has been saved by the antitoxin treatment would have acquired the power, by example, of secreting alexins, and by that means of maintaining immunity for the future, or if the moderate amount of irritation they would naturally experience from the activity of the bacteria before the arrival of the antitoxin would have taught them the art of so doing or not, because the antitoxin treatment has not yet been long enough known for the question to be answered; but it will be interesting to see how far people saved from death by this means are rendered immune or otherwise.

It is said that nothing very much is to be gained by this treatment either in mild or very severe cases, and there may be some truth in this as regards the former; but I am inclined to think that such severe cases run their course very rapidly, and that the period in which the antitoxin treatment would have any power is exceedingly limited and probably gone by

before it is attempted; again, these fulminating cases have no doubt been invaded by a far greater dose of bacteria than the so-called lethal dose.

In cases in which the antitoxin secures a foothold, and begins to exercise its power, we find a reduction in the severity of the symptoms, with a corresponding fall in temperature, though there may be possibly a preliminary rise; frequently rashes break out upon the skin some few days after the injection, but the reason of them is not yet known; the antitoxin is finally eliminated from the body, like all other waste, by the various emunctories; it has even been found excreted in milk.

The mode of use is by hypodermic injection by means of a specially manufactured syringe, every part of which can be taken to pieces and sterilized; there are several excellent patterns made in England, being all founded on that of Debove, which is the one in general use upon the Continent. Aseptic precautions are essential, and it is to be regretted that even the short exposure to the air during the operation of charging the syringe cannot be avoided; it is open to contamination from various sources. We shall see later on that our own syringe obviates this risk entirely.

The best place for administration is the flank, rather lower down than the region of the spleen; but if a large dose is employed, it is then better to divide the dose, giving a portion into each flank; the rate of injection should not be too hurried nor too slow, as the flow into the subcutaneous tissue is decidedly uncomfortable, and to children distressing; a little gentle massage over the spot aids absorption, and soothes the patient.

The quantity to be administered at a time is still rather an open question, but the tendency latterly is towards the administration of considerably larger doses than were given at first. No doubt the earlier cases received far too little, not much more than 1,500 immunity units being recom-

mended; now it has been found out that very large doses of antitoxin can be very well borne; and beyond the rash already mentioned, or some aching of the limbs, perhaps even a little effusion into some of the joints, there seems to be no reason why a large dose should not be administered at once, and, if Roux's standard is adopted, a commencement made with a full dose, according to the weight of the patient.

We have said (p. 48) that it is the toxalbumoses which contain the malignant poison, and that these are neutralized by antitoxins; but this antitoxin has no power over the vitality of the bacilli themselves. Now, the poison is not contained in the toxalbumoses in every bacterial fermentation, but often in the non-diffusible or feebly diffusible enzymes of the bacteria; hence arises the necessity of obtaining an antimicrobic serum—in other words, a serum which is capable of destroying the microbes themselves, for although their enzymes do not, as a general rule, travel far from the bodies of the bacteria which contain them, except in the two diseases before mentioned, yet these bacteria proliferate with such enormous rapidity that the result to the animal invaded is just as disastrous.

It happens that a serum *can* be prepared that will act as a destroyer of the vitality of this kind of microbe: it is prepared in a similar manner to that of the antitoxin serum; but, instead of the filtered toxins of the bacteria, it is the bacteria themselves that are injected, firstly in a defunct state, but later on the living bacteria are administered, and, finally, even living bacteria whose virulence has been exalted (by a process afterwards to be described). A serum prepared in this manner from an animal possesses extreme antimicrobic powers, but has little or no effect over the toxalbumoses.

The results of the antitoxin treatment have varied so much in the same and in different hands that it is difficult exactly to estimate its value: the disadvantages are, that it

can only be satisfactorily applied early in the disease ; that it is difficult to judge the quantity that should be administered in any given case ; that it requires special precautions in its mode of application, and that it is not by any means free from danger.

On the other hand, there can be no question that it has greatly reduced the mortality from diphtheria. A remark was made to me by one of the officers of the Medical Staff at Aldershot, to the effect that they did not now (since the general employment of antitoxin) dread diphtheria more than any other disease of childhood—a very different state of affairs to that which obtained before the discovery of the treatment by antitoxin. Upon the effect of antitoxin in other diseases, cases are being constantly published in the medical journals. One of the earliest cases of tetanus successfully treated in England came under the writer's observation in November, 1895, under the care of Dr. Walcot, of Camberley ; also a case of streptococcus fever after parturition, in which the specific microbe was discovered in the discharges before the inoculation. Neither of these cases could possibly have recovered under any treatment previously known. These three—diphtheria, tetanus, and puerperal fever—are the principal diseases in which antitoxin is of service ; upon its use in the second of these 'The Prognosis of Tetanus,' by Dr. George Worthington, in St. Bartholomew's Hospital Reports, will repay perusal. There are other diseases, equally deadly maladies, which number scores of victims to every one of the other three mentioned, for which no antitoxin is found, against which no animal is immune, and it is against these diseases especially that the treatment by pure ferments—first devised and practised by de Backer from selected and acclimatized yeasts—is principally, though not exclusively, directed.

The antitoxin treatment is interesting also from the fact that, as experiments have proved, animals immunized against

either vegetable poisons or snake venom are capable of yielding a curative antitoxin serum.

The principal theories on Immunity are those of Exhaustion, Retention, Acclimatization, that called the Humoral Theory, and finally Phagocytosis.

The Theory of Exhaustion.—When the bacillary fermentation begins to decline, it is supposed that the bacilli have used up all the food or pabulum of their predilection which can be found in the system, just as the yeast fermentation ceases in a poor wort when all the saccharine has been converted. Analogy may also be found in agriculture, for it is well known that a crop of wheat, grown on the same soil as a previous crop, exhausts that soil to such an extent that for the next season it must lie fallow, or be planted with some other crop, before the elements required by the wheat-plant for its growth can be restored. Opponents to this theory of exhaustion maintain that it is quite disproved by the fact of passive or indirect immunity (p. 57), and that it would be absurd to suppose that a small quantity of exhausted pabulum serum could exhaust the pabulum found in the tissues or serum of the infected animal. I am not prepared to admit the completeness of the disproof, for it is reasonable to think that, as the addition of alcohol to a wort in fermentation will arrest that fermentation, it may be that the exhaustion theory is true as regards the amount of pabulum that the ferments are capable of dealing with, but that, as in the case of the more richly saccharine wines, there is much fermentable matter remaining, though the ferments are unable to deal with it, being inhibited by the action of their own excretions, which brings us insensibly to the next theory,

The Theory of Retention, or antidote, which assumes that the excreta or life-products of the bacteria causing the disease, which excreta are inimical to their growth, are also inimical to the growth and development of other and future bacteria of the same variety, and that these life products, which have

already inhibited the activity or destroyed the vitality of the producers, leave them a prey to the natural defenders of the body in which they themselves are retained indefinitely.

The Theory of Acclimatization, or acquired tolerance, supposes that the cells of the economy get habituated or accustomed to the action of the life-products of the bacteria until, finally, they are no longer troubled by them. Both the animal and vegetable kingdoms afford numerous examples of successful acclimatization ; also it will be shown later on that we can habituate our formed ferments to the action of bacilli, such as the tubercle bacillus, until they are no longer incommoded by its presence.

The Humoral Theory takes for its hypothesis that certain changes take place in the serum and other fluids of the body. It had been known that normal blood serum possessed certain bactericidal properties, as has already been stated, but that these properties varied in different animals, yet did not vary with the immunity enjoyed by the different animals, neither did the variation of the properties follow any law. A series of experiments have proved that these bactericidal properties are due to the presence in the serum of a substance called 'nuclein,' which could be extracted from it, and was found to possess these properties. Nuclein is normally but variably produced by leucocytes of all kinds, especially of the blood, and I cannot help thinking that the amount and activity of this production is largely guided by the influence of the nervous system, in spite of the fact that physiologists have not yet demonstrated the action of the nervous system, either over the connective tissues with their cells, or over the plasma and cells of the blood. It is beyond doubt that, besides the nuclein normally secreted, certain other substances of similar composition, called alexins, are secreted by the protoplasm of leucocytes when they are irritated by bacterial fermentation ; they are chiefly furnished by the leucocytes of the spleen, lymphatic glands, and other structures rich in leucocytes.

Those of the blood have other duties to perform, but may also help in this. Alexins are proteid bodies, and may be divided in sozins, which are normally present in the serum of animals in a healthy state, and consist of mycosozins, which destroy the bacteria, and toxosozins, which neutralize their products. These are the natural defences against invasion; the other division consists of phylaxins, which are present in artificially immunized animals.

The Theory of Phagocytosis.—In the first chapter we had occasion to point out the particular structure of the leucocytes, and draw attention to their power of throwing out pseudopodia, by which they were enabled to travel, or inglobe any foreign particle which may come within their reach. What we then stated generally must be now reduced to its bearings on a particular line. It was discovered by Robert Koch, during his experiments on the minute bacteria of mouse septicæmia, that these minute micro-organisms could be inglobed by the leucocytes in the same manner as other organic particles; but it was left to Metschnikoff to work out the whole theory of phagocytosis. He found that this property was not only enjoyed by one class of cell, but others; that in the human body the principal phagocytes, or cells possessing the power of devouring other bodies, are of two kinds: (1) Large polynucleated leucocytes, which are leucocytes of the blood, possessing a multipartite nucleus. These are also termed 'neutrophile cells,' from the resistance they observe towards stains; they were termed by Metschnikoff 'microphages.' The other kind he called 'macrophages,' which include the large mononucleated leucocytes of the blood, the cells of the endothelium, and the connective-tissue corpuscles. Metschnikoff's experiments were first undertaken with the large bacillus of anthrax upon frogs, which are normally insusceptible to the disease. He found that directly the bacillus was introduced into the circulation of the frog, the phagocyte leucocytes nearest to them at once crowded round and engaged

them, throwing out processes, which surrounded them, and then withdrew them into the cell, which thus inglobed them, and finally digested them. If the phagocytes happened to be in insufficient quantity to deal with the intruders, then intelligence of the fact seemed to be rapidly transmitted by some means, for others came hurrying to the spot until a local leucocytosis was produced, surrounding the bacilli and preventing their escape into the general circulation until inglobed by the phagocytes nearest to them. This attraction possessed by the phagocytes to the bacteria is called chemiotaxis ; it is called 'positive' when the cells are attracted, and 'negative' when they are repelled, though it must be remarked that this repellence is not absolute, and probably exists only for a time. In cases where neither attraction nor repulsion can be ascertained, the chemiotaxis is said to be neutral, though this appears to be a somewhat unnecessary term. Motile bacteria do not wait to be attacked, but on their own account attack the leucocytes, and a veritable struggle for the mastery ensues, many leucocytes being killed in the action.

Metschnikoff also observed another point of great scientific value, that the phagocytic power of the cells of an animal varied according to the power of immunity enjoyed by that animal ; therefore the phagocytic power in susceptible animals is exceedingly limited. Furthermore, he also observed that the cells of animals naturally susceptible, but protected by a process of direct immunity, acquired additional phagocytic powers, probably from being acclimatized or accustomed to deal with feeble invaders, and hence had become strong enough, by training, to inglobe later comers even though possessing greater virulence. These last two observations of Metschnikoff have a very great bearing upon the theory of our treatment by pure ferments, as will readily be seen when we come to demonstrate the phagocytic power that they themselves possess. The question, however, still

arises as to whether the phagocytosis is the cause of immunity, or is called into activity because of it.

On considering the various theories with as unbiassed a mind as is possible to us, I think we may safely say that none of them, taken singly, can alone account for immunity, but that they all, especially the two last mentioned, enter as factors to bring about an exceedingly complex process ; that the term 'immunity' probably covers dissimilar as well as similar biological, not chemical, processes, by which the natural defences of the body are brought into their full power, or even increased by art. Not amongst the least of these factors is the state and influence of the nervous system.

CHAPTER IV.

PHAGOCYTOSIS BY FORMED FERMENTS.

On examining the ordinary yeast of commerce, under the microscope, cells may be seen containing ascospores or endogenous buds within them, such as we have already described; besides these may also be seen a number of small specks that have been called pigment, but whose real nature has not until recently been discovered: though their existence has been known for a long time, yet it seems never to have been remarked that some of these specks possessed motility. They are found to be more numerous in a specimen taken from the periphery of a lump of yeast than from one taken from its centre, and they are much more common in an old yeast than in a fresh specimen. In a perfectly pure culture these specks are never seen (see illustration, p. 16), but if such a culture be exposed to the air for any length of time, the cells will be found to contain these specks or pigment. Some authors have considered these specks to be minute globules of fat, but on insufficient grounds, which can easily be proved by spreading a thin layer on a glass slide, and washing it ten or a dozen times with æther; if the specimen is then stained and mounted, the specks will be seen to be within the cells just as they were before; clearly, therefore, they are not fat. The same kinds of specks or pigment may be seen lying free outside the cells as well as imprisoned within them. In order to make very sure, the æther test was applied more stringently. A

trace of commercial yeast about as big as a pin's head was first examined under the microscope, and the pigment noted to be present; it was then placed in a test-tube with a hundred times its weight of æther, and left, with occasional shaking, for twenty-four hours; at the end of this time the æther was decanted off, and when the æther was evaporated off, a specimen of the yeast was stained and examined afresh; the pigment was still there. If not fat, what could these specks be?—for they were certainly no part of the normal constituents of the yeast cell. Their true nature was accidentally discovered by M. Bruhat, an analytical chemist of Paris; the story of the discovery is as follows:

At the beginning of the year 1892, a certain M. Slizewicz, a pharmaceutical chemist of Cette, in the South of France, sent some bottles of fig wine to the Société Française d'Hygiène for the purpose of ascertaining if the ferment was of any specific nature. During the carriage one of the bottles got cracked, and the wine within had partly turned to vinegar; however, it was examined as well as those which were sound. The ferment was found to be one of the species of the *Saccharomyces Pastorianus*, and in the spoilt wine, besides these cells, were seen many vibrios of the *Bacillus aceti* lying free in the liquid; but this was not all, for in this specimen a great number of these vibrios were actually seen inglobed within the yeast cells; furthermore, it appeared that some of them had undergone a species of digestion, or marked change of some kind, as these were stained with great difficulty. There could be no doubt that the vegetable cell of the *Saccharomyces Pastorianus* had acted towards the *Bacillus aceti* exactly in the same manner as a leucocyte would do in the presence of a microbe; the bacilli were actually *inglobed*; some of them were partly digested, and others that were only partly inglobed appeared to be much swollen or enlarged at their free end, as if they had caused their protoplasm to flow

back to that end, in order to escape from the cell which was gripping and holding them.

The true nature of these specks and pigment was now apparent, and yeast cells had demonstrated themselves to be phagocytes. It appeared plain, henceforth, that these pigmentary specks were the result of the introduction of particles taken in from the surrounding medium, or even perhaps the débris of bacteria partly digested by the intracellular diastases.

We have already given, in the preceding chapter, a cursory glance at the theory of phagocytosis in its relation to immunity, and, as there promised, we shall now necessarily enter a little more fully into this subject, the better to understand that which we shall have to say afterwards concerning the phagocytosis by formed ferments.

In the war between the leucocytes and bacteria, the latter revenge themselves for their inglobement by endeavouring to poison the former by means of their enzymes, or intracellular poisons, which paralyze the digestive action of the leucocytes. The fight is now pretty close, and if the leucocyte is far from its source of supply it dies; but if not, it sets itself to work to secrete matters which neutralize the bacterial enzymes, the microbe being finally digested. Leucocytes have not a universal phagocytic power over all species of bacteria, for those of an animal susceptible to a certain disease are quite unable to inglobe the bacterium producing it, even when placed in contact, unless the animal has been rendered artificially immune, as described in the last chapter. Leucocytes may inglobe bacteria in a state of virulence; for instance, Koch's bacilli of tuberculosis, injected into rats, which are somewhat refractory to this disease, are at once taken up and inglobed by their leucocytes, yet should these bacilli already inglobed, but not yet destroyed, be injected into a susceptible animal, like a guinea-pig, a fatal tuberculosis is the result; it

follows, then, that the bacilli must have been inglobed whilst in a state of virulence.

Bacteria which have been inglobed, but have failed to poison their host, have to submit to the influence of the protoplasm of the leucocytes; it has often been seen that the red corpuscles of the blood, when inglobed by the white ones, gradually dissolve, leaving only a pigmentary residue. Not only does this happen with red corpuscles, but with any other cell that has played its part in the economy and has to be removed; such cells gradually lose their vitality (shown by being stained with difficulty), and disintegrate into fine granules. These changes must be put down to intracellular digestion; indeed, diastases capable of digesting proteids have been isolated from the leucocytes. The intracellular digestion of bacteria can be specially well observed and studied in animals that are refractory to or immune against any disease, the last part to be digested being the resistant cell wall. It is not to be supposed that all the microbes thus inglobed are digested and destroyed, for we see just the contrary, more especially in diseases in which the bacteria are very small, such as tubercle, measles of pork, mouse septicæmia, and influenza, the micro-organisms of the two latter being particularly small. In such cases the leucocytes may inglobe the greater part of them, and digest many of them; yet others will escape into the general system. Those that have been inglobed by a leucocyte naturally feeble, or too far away from its nutrient supply, find that they are able to overcome the digestive faculty of the leucocytes by their own toxic secretions; they are then carried off by the sickened leucocyte to other parts of the system, where the leucocyte finally dies, but the microbes emerge from their captivity, and begin their toxic fermentation in a new quarter, though it is probable that they themselves have lost vigour in the struggle. Hence it follows that, although the phagocytic power of the leucocytes may not be sufficient to cope with all the invaders,

still they enable the system to make a good struggle against them, retard the rate of their progress, and so gain time for alexins to be formed, or at least delay the fatal period, which arrives when the system is exhausted by the struggle, and, having lost its garrison, surrenders and dies; another chance is given by this retardation by the phagocytes, as it gives a certain time during which the physician may exercise his art.

In order to ascertain whether the yeast cells had phagocytic powers over other bacteria, as well as the *Bacillus aceti*, the following experiments were made:

Experiment I.—With Bacterium Termo.

A piece of liver was chopped up and macerated in distilled water for some hours; the solution thus obtained was filtered through a Chamberland filter in order to rid it of all formed elements; the filtrate, limpid and colourless, was collected in a Florence flask, and exposed to the open air; forty-eight hours afterwards it had acquired the characteristic odour of putrefaction, microscopic examination showing a large quantity of small motile bacilli rapidly multiplying. Twenty c.c. of this liquid were next placed in a small flask with half the quantity of backérine,* and the whole left in a suitable temperature to ferment. Four hours afterwards the appearance of little bubbles of gas announced that alcoholic fermentation had commenced; twenty-four hours afterwards the liquid was in full fermentation, with the fresh and agreeable odour of alcohol, which had replaced the unpleasant smell of the day before; the next day the fermentation was ended, and the liquid allowed to remain in the flask. For a fortnight no change was observed, after which numerous white colonies appeared on the surface of the liquid, which again gave off the same putrefactive odour as at first; the mixture was examined under the microscope—

* Pure yeast cells mingled with a certain definite proportion of fermentable and mineral matter necessary to fermentation and to the life of the cells.

1. Three hours after the addition of backérine ;
2. Forty-eight hours afterwards, when the fermentation had ended ;
3. A fortnight afterwards, when putrefaction had recommenced.

The first examination was carried out by making an unfixed cover-glass preparation, stained with methylene blue. The yeast cells were not stained, but the bacteria were of a lilac tint, and very motile ; some yeast cells already contained bacteria within them, but these were much less deeply stained than those lying free in the liquid. Some, indeed, of the inglobed bacteria were not stained at all. One bacillus was partly within and partly outside a yeast cell ; it was deeply stained, so it could be very distinctly seen that the free extremity was rapidly vibrating in the surrounding liquid ; the microbe seemed to twist itself upon its long axis in a sort of screw-like manner, sometimes rolling to one side and sometimes to the other, but never turning completely over; it worked its way gradually through the cell wall, until suddenly the forward movement ceased, and a retrograde movement began, by which the microbe withdrew itself from the cell as if it had found the contents less pleasant than it had at first imagined. Another yeast cell was engaged with two microbes, which were endeavouring to penetrate it, already having partly done so. It was clearly noticed that the part of the microbe actually passing through the cell wall was much more pinched in and thinned than at either of the extremities, and that this thin part did not show any stain, as if the microbic protoplasm was collected at either end, and could only flow with difficulty through the narrowed portion that was gripped by the cell wall ; after a time both bacteria had succeeded in penetrating, being both entirely within the cell, where they preserved their motility for some time, after which they appeared to swell, and barely move at all ; finally all movement ceased. One bacillus remained in a crescentic

shape, lying along the internal wall of the cell; the other lay straight in its middle, and appeared to divide it into two parts. It was very interesting to watch the attack of the bacteria upon the yeast cells, which appeared to play quite a passive part. The attack was always oblique to either axis of the cell; that is, it was always a flank attack, never frontal, their tactics being quite in accord with the teachings of modern war. But the opinion borne upon me is that penetration can only be effected by a kind of diagonal passage, perhaps resembling that of the inguinal canal, and that the bacterium accomplishes its object in a sideling, sideways diapedesis similar to the manner in which a leucocyte finds its way through a bloodvessel without any escape of the contents thereof, as mentioned in Chapter I.; it is certain that the microscope can show no solution of continuity in the cell wall after penetration. It does not follow that the first attack on the yeast cell is successful, in which case the attack is renewed either on the same cell or on another one.

These observations showed that the inglobing of the bacteria took place *before* the commencement of active alcoholic fermentation, and at a time when the bacilli were in full activity; also that the bacilli were the assailants of the yeast cells, which, although at first playing a passive rôle, soon reacted against its invader by bringing to bear on it the action of its intracellular enzymes, the first evidence of which is shown by the recoil and withdrawal of some of the bacilli; this withdrawal only seems possible in cases where the bacterium has not penetrated very far. When complete penetration has been effected, no bacterium has been observed to make its way out again, although a vigorous attempt at this may be made by dashing themselves against the internal wall; but whether they get weakened by the chemical contents of the saccharomyces cell, or that the cell walls are constructed like valves, permitting ingress, but not egress,

except by the will of the cell, we do not quite know. After having been inglobed for some little time, it is curious to see how the protoplasm of the microbe collects at either end, leaving the middle part almost colourless. In no case was there seen any multiplication by fission in any inglobed bacterium.

The second examination, made when the alcoholic fermentation had finished, was conducted in a similar manner, and cover-glass preparations made; the bacteria, lying free in the liquid, appeared motionless; many were inglobed within the yeast cells, which were in the actively budding state. It was noticed that the inglobed bacteria were not stained, although the surrounding fluid, being very alcoholic by reason of the fermentation, would naturally conduce to free staining, which showed that the inglobed bacteria were dead.

For the third examination cover-glass preparations were made in a similar manner to the first two; the bacteria were seen to be well stained, and actively motile, but the yeast cells dead, or in a condition of degeneration, either in the form of hyphomycetes, or anastomosed into a kind of mycelium containing conidia; although the bacteria were actively motile, they seemed to take no notice of the yeast cells, and did not attack them in a single instance.

Experiment II.—With Mixed Bacteria.

A specimen of diabetic urine was exposed to the air for three days after emission; by that time it had become neutral in reaction, and contained both cocci and bacilli, freely motile and in considerable quantity; it was of a disagreeable odour; as the liquid contained glucose by reason of its diabetic origin, pure yeast alone was used, instead of backérine, as in the former experiment; it was added about 6 p.m. The next morning alcoholic fermentation was in full swing, the mingled urinous and putrefactive odour of the

day before being replaced by that of alcohol; the reaction of the fluid was now acid. A cover-glass preparation was made therefrom, and examined microscopically; a large number of healthy, vigorous yeast cells were seen in active gemmation, numbers of them containing both bacilli and cocci inglobed within them; the bacteria lying free in the fluid appeared to be motionless. As in the first experiment, the liquid was left to itself; in ten days' time it was found to have undergone acetic fermentation, and the odour of putrefaction was again apparent. A preparation made from this showed numerous bacteria, motile and active; but the yeast cells were either dead or in process of degeneration.

Experiment III.—Staphylococcus Pyogenes Aureus.

Some sterilized bouillon was impregnated with a fresh culture of the staphylococcus on gelatine, from which a growth was quickly obtained; the bouillon was divided into two portions, each being introduced into separate tubes, previously sterilized, marked A and B, which were immediately plugged with cotton-wool, after the addition to each of an equal volume of backérine, which had been previously examined under the microscope; the *Saccharomyces cerevisiæ* was the yeast used in this case, and the protoplasm of the cells appeared homogeneous and free from granulations.

The tube A was left alone for two hours and a half, when a drop was taken from it and examined; only one or two cells of the yeast were as yet seen to be in a state of gemmation; many of them still appeared homogeneous and without granulations, but the majority of them contained in their interior from one to eight, and in one instance twelve, staphylococci; very many of the staphylococci were free in the surrounding liquid. The microscope was then inclined towards the observer, when all the organisms were set in motion according to their gravity. The outline of the yeast cells was very distinct, and this tilting of the stage proved beyond

all doubt that the staphylococci were actually within the cells, and not merely sticking to their outside, although there certainly were some in this condition, but the appearance was quite different, for as the yeast cells rolled about their contour was seen to be studded with little knots like granulations, some of which were seen to be washed off from their hold; this was the more easily seen when the specimen was very slightly stained, the free staphylococci and those adhering to the cell walls being of a lilac or violet tint, whilst most of those inglobed, and so submitted to the intracellular diastases of the yeasts, remained unstained.

The tube B was left to itself, at a temperature of 24° C.; four hours afterwards some gas bubbles appeared, showing that fermentation had commenced. The next day the fermentation was nearly over, and the liquid had the sweet, fresh odour of alcohol. Two specimens were taken and seeded on to gelatine, but both failed to produce any culture.

Experiment IV.—Diphtheria Bacillus.

Some sterilized bouillon, with 5 per cent. of glycerine, was seeded with an old culture of diphtheria from a false membrane containing micrococci, as well as the Klebs-Löffler bacillus. A few days afterwards the liquid became turbid with numerous white colonies. An equal quantity of backérine was now added to it, and the mixture maintained in a temperature of 20° C. Four hours afterwards fermentation commenced; the next day it was ended, and the frothy head subsided. The contents of the flask were then well shaken up, a preparation made and examined. Numerous yeast cells were seen gorged with both cocci and bacilli, especially the former; many of both kinds were also lying free in the liquid. Preparations made from this fermentation stained but poorly with the methylene blue, but were very well stained by fuchsine.

A similar bouillon, seeded with a *fresh* culture of the diph-

theria bacillus, treated in a similar manner, gave the same results as regards fermentation and microscopical examination, with the exception that, in this case, there were no cocci present.

Experiment V.—Tubercle Bacillus.

One c.c. of a pure culture of Koch's tubercle bacillus was placed in a sterilized flask with the same quantity of a pure culture of the *Saccharomyces cerevisiæ*, and to this mixture sterilized distilled water was added until it measured 5 c.c. ; the flask was then placed in the incubator, and left there for eighteen hours at a temperature of 37° C. It was then examined. Many of the yeast cells were in the ascomycetic form ; in some cases the ascospores were numerous, but very small ; in others the protoplasm showed vacuoles, some cells appearing to be quite empty, with the exception of a kind of nucleus, sometimes with a nucleolus. A few conidia were present, also some cells of a hyphomycetic character. Numerous tubercle bacilli were seen lying free, either singly or in parallel rows of twos or threes ; some were also seen inglobed within the yeast cells, of which some presented rather interesting peculiarities. One large cell of an elongated, ovoid shape showed, at one extremity of its long axis, a highly stained tubercle bacillus which had partly penetrated within it, whilst at the other extremity the protoplasm seemed to have collected itself against the inner wall, leaving the rest of the cell empty. The protoplasm had the appearance of a large nucleus with nucleolus. This is especially interesting, as it so closely resembles the phenomenon which obtains in the formation of a giant cell in tubercular tissue.

The specimen was very clear, as the bacillus and nucleus were alone well stained ; the rest of the cell was not, though both outer and inner walls were very distinct. To make sure also that the bacillus was actually and really within the cell, and not lying on or beneath its surface, an accurate

focus was obtained, in which both bacillus and nucleus showed their maximum colour equally, as well as their sharpness of outline. The micrometer screw was now turned alternately, so as to raise or lower the objective, the effect being in each case to make the microbe disappear first, whilst the nucleus merely lost its sharpness, but was still visible, being of a considerably greater thickness than the bacillus. These manœuvres showed that the microbe was not simply adherent to either the superior or the inferior parietes of the cell, but was existing on a plane with its centre, and therefore actually within the cell. Another cell, close by, showed something similar, but in this case the cell was a round one, and the protoplasm appeared as a nucleus with nucleolus in the *centre* of the cell, which contained two bacilli—one each side of the nucleus—lying in the vacuole between it and the cell wall. The majority of the yeast cells contained ordinary ascospores, though many of them were quite choked up with numerous tiny spores.

Dr. de Backer's explanation of the ascospore formation is that pure yeast was added without any nutriment, and maintained for eighteen hours in the incubator at 37° C. (*vide* p. 18). In addition to this opinion, I may add that my own experiments show that, at whatever temperature such a mixture is maintained, when pure yeasts only are mingled with a culture of the tubercle bacillus, *without saccharine*, we always get the formation of ascospores.

Experiment VI.—Tubercle Bacillus.

In this experiment the same conditions were observed as in the last, with the exception that backérine was used instead of the yeasts alone, and the mixture was fermented at the room temperature only. The fermentation was rapid and abundant, and when finished a preparation was made from it and duly examined. Most of the cells were in the process of gemmation ; scarcely any of the hyphomycetic form were seen,

but none of the phenomena noticed in the last experiment could be ascertained in this one. The only interesting point noticed was that a good many of the tubercle bacilli seemed segmented, like a straight chain of four or five small streptococci, a form not infrequently seen in the sputa of phthisis. After treatment by pure ferments, this appearance is common, denoting the decadence of vitality in the bacillus. The examination of another preparation from the same specimen, taken later, afforded some interesting phenomena. The test-tube containing the fermentation had been uncovered several times, so that air had got in in spite of quick replugging; also the yeast cells were commencing to degenerate, owing to the conditions of the experiment, consequently numerous colonies of foreign microbes had developed somewhat rapidly, amongst them being a small, short bacillus, of a length about twice or thrice its breadth, with a contraction or thinning at its centre, very motile, and being easily stained with an acid stain. Around some of the yeast cells, a number—sometimes a very considerable number—of these bacilli had taken up such a position as is seen when a magnet is placed amidst steel filings. One such cell was surrounded by more than forty bacilli, arranged like the spokes of a wheel, with one end fixed at a tangent to the surface of the cell wall, the other end remaining free, and still motile. The cells thus surrounded were gorged in their interior with the same microbes.

We must now see what conclusions may be legitimately drawn from these experiments. We may safely say that when yeast cells and bacteria meet in a common medium a very strong mutual antagonism arises, which leads to an attack by the bacteria upon the yeasts; these allow themselves to be penetrated by the former, then each tries to poison the other by their respective intracellular enzymes, the result being that when the opposing forces are in anything like equality, the yeast cells invariably obtain the mastery, duly digesting the bacteria, after which or during which they

proceed to carry out their own natural functions, for we have seen that the presence of bacteria in no case prevented or delayed alcoholic fermentation. We are also justified by saying that this statement applies to all bacteria, both bacilli and cocci, to pure saprophytes like *Bacterium termo* as well as to virulent pathogenic micro-organisms such as the diphtheria bacillus, also to the motile bacteria equally with those, such as Koch's bacillus, which are non-motile. We may further say that, as long as the yeast cells are vigorous, they prevent the fermentative action of bacteria generally. The first and second experiments showed that the phenomena of putrefaction were entirely stayed by their action ; the third experiment showed that staphylococci were so influenced by the yeast cells that they were either destroyed by them or at least rendered incapable of reproducing or multiplying when transferred to a favourable medium. It must be acknowledged that it is the young and vigorous cells that are true phagocytes, and that the pigmented bodies or specks seen in the cells of commercial yeast are really the remains of microbes broken up and digested by their intracellular diastases.

This power of phagocytosis is not only possessed by the Saccharomycetes, but also by the conidia of some of the Mucorineæ ; indeed, some authors go so far as to say that the whole family of Saccharomyces is nothing more than vegetative or spore forms of higher fungi. Whether that can be proved or not remains to be seen, but they certainly present many points in common with the conidia of hyphomycetic fungi.

The following experiments were made : Several flat-bottomed flasks were charged with a thin layer of fermentable matter, to which a little yeast was added ; when the alcoholic fermentation had ceased, the *Bacillus aceti* was added to each flask in different doses. In those that received only a small dose the acetic fermentation was a long time in taking on, but in those which had received a large dose the

action was much less delayed. When the secondary fermentation was ended, the flasks were seeded with cultures of Mucorineæ, also in different doses. In those that received but little, either the Mucorineæ did not develop at all, or only very slightly, the *Bacillus aceti* being seen to be very motile; in the other flasks, however, the moulds developed well, and the liquid lost its penetrating odour of vinegar, to acquire an agreeable perfume like that of meadow flowers, daisies and sweet clover; it was evident that a peculiar ætherization had taken place under the influence of the developing fungi, which had also inglobed the *Bacillus aceti.*

It was found that if, in a suitable wort, yeast cells and the *Bacillus aceti* were introduced together, the alcoholic fermentation progressed without hindrance from the *Bacillus aceti*, which had no power to convert the nascent alcohol, yet it nearly always happened eventually that acetic fermentation took place, at first slowly, then rapidly, the explanation being that the yeast whilst young and vigorous inglobed most of the *Bacilli aceti*, but that when the yeast cells had finished their work, and there was no longer any saccharine to furnish food for them, those *Bacilli aceti* which had been left free regained sufficient energy to exercise their functions and multiply without troubling themselves about the worn-out yeasts.

From these experiments conclusions were drawn that, in the struggle for existence between micro-organisms, it is necessary to bear in mind two things: first, the quantity and quality of the adversaries, and, secondly, the chemical nature of the medium. It is owing to variations in these two conditions that a few individuals of the primarily defeated and conquered species are allowed to exist in a latent condition, gain a foothold, and eventually occupy the whole medium, when it has become, by change of its constituents, unfit for, or less favourable to, the development and activity of the species that were at first victorious.

It remains, then, to consider what happens when the yeasts are not in numerical superiority, or even equality with the bacteria, or perhaps in a considerable minority. What happens naturally is that the phagocytic yeasts do all they can and then finally perish, whilst the bacterial fermentation, acetic, lactic, butyric, putrefactive, or whatever it may be, continues freely. The same obtains exactly within the animal economy ; if the natural defenders of the body are overcome, and the bacteria can evolve toxins faster than the tissues can excrete their alexins, then the victory must rest with the bacteria. It fortunately happens that the system, temporarily overcome by the suddenness of the attack, rallies and calls up its large supply of reserve forces.

The object of the laboratory and experimental work upon which we are now engaged is to ascertain exactly how to support and reinforce these reserves with a third line—the first of which is phagocytosis, the second the humoral formation of antitoxins, the third we shall provide by throwing into the system, at the time of its need, a new army of phagocytes and nucleins.

In order to get a complete idea of phagocytosis in all its bearings, we should devote a little space to the study of its application in scientific wine-making, for which purpose we shall turn to the works and letters of M. George Jacquemin, of Nancy, the greatest authority in France on the subject of yeasts, one whom M. Pasteur always considered to be one of his most brilliant disciples. In a letter to Dr. de Backer, he says that he was examining a yeast that had just been prepared in a certain distillery, when he pointed out to the distiller a quantity of bacteria present, nearly equalling the cells in number, consequently he directed him not to make use of it. Out of simple curiosity the distiller preserved the yeast for a week. When M. Jacquemin returned, the distiller then called his attention to it, and showed him that the bacteria had nearly all disappeared ; he could with difficulty find one.

This much astonished him, and he could not account for it at all, for at that time he was unaware of the discovery of De Backer and Bruhat on the phagocytic powers of yeasts.

In one of his latest works he says, in speaking of spontaneous fermentation, that the spores of yeasts, moulds, and bacteria develop together, and participate more or less in the same mode of existence, the bacteria especially taking up a large proportion of the saccharine nutriment. Then commences and is maintained a struggle for existence between the yeasts and the bacteria, the latter being the greatest foes to the generation and future prospects of the wine. The bacteria, no doubt by instinct, attack the saccharomyces in order to get entire possession of the saccharine nutriment. The struggle has already been described. It would seem that the object of penetrating the saccharomyces cell is that the bacillus may dwell there in comfort, just as the vampyrella invades the cells of the filamentous seaweeds. In this, however, they often deceive themselves, as is shown by the little fishes which penetrate the ampullæ of certain seaweeds and die there; also the very instinct which causes the fly to alight on the leaf of a drosera, or to enter the corolla of a *Carica papaya*, leads to its destruction. The bacillus may be equally surprised and disappointed when it gets inside the phagocytic yeast cell, as the fly when the carnivorous plant has imprisoned it, and commenced to digest it. The saccharomycetes which have been thus invaded, and which have exhausted their strength in defending themselves and digesting their adversary, may be for a time deprived of their original physiological activity, and so unable to withstand a fresh assault. It follows, then, that if the bacteria can prevail by numbers they will remain masters of the field, upon which alcoholic fermentation will cease and bacterial fermentation will take its course, with the differences characterized by the names given to the various diseases of wines. An instance of bacterial victory occurred in a large distillery, where

15 hectolitres, about 330 gallons, of malted wort was accidentally allowed to ferment spontaneously. It was examined under the microscope, when quantities of bacilli (lactic and butyric) were seen. Unwittingly, and whilst M. Jacquemin's back was turned, a workman poured the whole of this into a large vat containing 800 hectolitres of a wort of molasses in full fermentation by a pure yeast, with the result of immediately arresting the alcoholic fermentation. In this case the quantity of bacteria was too great in proportion to that of the yeast; the whole amount had to be immediately distilled in order to save what alcohol they could.

When it is the saccharomycetes that enlist the big battalions on their side, the vanquished bacteria disappear and alcoholic fermentation follows its regular course. In this case the wine will be good, and will keep well.

When the grapes have been pressed, and if the juice is left to a natural or spontaneous fermentation, how can anyone foresee what kind of fermentation this will be? The vine and its fruit, especially the stalks, give lodging to many germs and micro-organisms deposited there by the air and by flies, and there is nothing to warn one to which side the balance will turn. Natural fermentation is subject to many risks, and gives no security to the viticulturist, who knows this well, by experience often bitter, and feels that he is groping in the dark in spite of all the care and labour he may expend on his work. This insecurity certainly deserves the intervention of science, which alone can solve the problem of the amelioration of the wines by a natural process, thus putting the viticulturist in a position to sell his produce without difficulty, and to furnish the very best wines for table without materially raising the price. Science has now accomplished this, but how? By rendering the viticulturist master of the fermentation, directing him in the paths of light, and teaching him that he must necessarily mix the pure and selected yeast of wine, chosen according to the nature of the grape,

with the wort in proportion to the pressing ; for this yeast, being full of vigour, and in a medium of predilection, would seize upon the whole wort, put an almost insurmountable barrier to the development of deleterious germs, and give the fermentation such a direction that the results would be exceedingly favourable, and answer all his expectations.

Again, suppose a wine turns slightly, or, in other words, becomes invaded by the *Bacillus aceti ;* to-morrow it will be vinegar. But this can be prevented by adding to it a small proportion of a pure yeast. A few hours will see alcoholic fermentation re-established, and that the *Bacillus aceti* has disappeared by phagocytosis ; thus the wort is cured, and will become good wine.

The reason of all this is that yeasts gain in physiological power by selection and cultivation, and by this exaltation are enabled to dominate, neutralize, and prevent the evolution of ferments pathogenic to the wine, which are contained in most worts, either derived naturally or accidentally. Thus diseases due to these latter are prevented, and the wine assured in its keeping qualities, or in what we should term in animals their good health.

We have now seen how very similar are the fermentations produced in the vegetable kingdom to those produced by bacteria within the animal economy ; we have studied the question of immunity and natural cure in diseases of both animal and vegetable fermentations ; we have seen much the same principles involved in each, especially that of phagocytosis which in the case of yeast cells is by no means limited to the bacilli of acetic or kindred fermentations, nor even to the purely saprophytic bacteria, but extends in full power to the virulent pathogenic bacteria that persecute the human race, including the deadly tubercle bacillus of Koch, which is responsible for a seventh part of their total mortality ; we have also seen how the diseases of wine may be cured by the proper application of pure and selected yeasts : surely, there-

fore, it is reasonable to expect some good results by applying the same process to the treatment of microbic diseases in the human body. The blood, or 'human wort,' a complex fluid, equal in quantity to a thirteenth part of the weight of the body, becomes invaded by bacteria just as the ordinary must of wine or wort of beer; the one is the pathological fermentation of certain animal juices, the other that of vegetable fluids; from the same causes are produced the same effects —even more, the same reactions; the analogy is complete, absolute.

It is perfectly reasonable, and founded on scientific data, to propose the application of the physiological properties possessed by yeast cells, enhanced and exalted by selection and cultivation, by injection into the animal economy, for the purpose of opposing and neutralizing the pathological action of virulent bacteria which have invaded it, especially those against which no animal is immune, and for which no antitoxin can therefore be prepared. This is the aim and object of our work; the future alone will show the full results to be obtained, but even as yet we have reason for a certain satisfaction in the results already obtained, with a great hope that we have entered a port to a land of promise hitherto untrodden and unexplored.

CHAPTER V.

PURE YEASTS: THEIR PREPARATION AND THE APPARATUS FOR THEIR ADMINISTRATION.

Experiments upon animals were very nearly being abandoned, and the whole subject given up, because, in spite of every antiseptic precaution possible, the injections produced painful indurations or abscesses at the spot of inoculation. On one occasion a very hard swelling was caused by the intra-peritoneal injection of 10 c.c. of a solution of yeast into a guinea-pig, which lost 120 grammes of its weight in a few days; this swelling took nearly a fortnight to subside. In order to make sure that the antiseptic precautions were absolute on injection, the method adopted in one case was by means of a Ziegler's cell with a very fine tube kept for four hours in the subcutaneous tissue. Microscopic examination showed us that an abundance of leucocytes had invaded the region of inoculation, but we were also made aware that the yeast cells contained numerous granulations and actual bacteria. A direct microscopical examination of the yeasts of which we were making use revealed all sorts of impurities, bacteria and foreign bodies of many kinds, including several distinct kinds of yeasts. We turned our attention to a classical work on the micro-organisms of fermentations, by Joergensen of Copenhagen, illustrated from Nature by Holm. The author says: 'The *Mycoderma cerevisiæ*, studied by Hansen, that is generally found in the breweries of Copen-

hagen, assumes various forms of cells. In each cell there is generally seen one, two, or three small, very highly refracting specks which frequently show a tremulous or rolling movement.' There is a drawing by Holm (Fig. 5) illustrative of this, to which the reader's attention is drawn, for it reproduces exactly what we have seen hundreds of times in yeasts that were supposed to be commercially pure, yet there is a slight error, or rather omission, for it is very rare to find these little specks inside the yeast cells without noticing them outside as well; perhaps, as the artist was only delineating yeasts, the



FIG. 5.—COMMERCIAL BEER YEASTS.

A copy of a drawing from nature by Holm in Joergensen's work, 'Traité des Micro-organismes de la Fermentation,' Paris, 1895. Dangerous for therapeutical purposes.

little specks outside, of whose import he was quite unaware, were deliberately left out. Neither Holm nor Joergensen gives any explanation regarding these little specks, perhaps from not having paid any attention or attached any importance to the same appearances outside the cells, although those outside may be motile. Now, we have shown in a previous chapter that these little specks are really bacteria in various stages of intracellular digestion, and if the reader will turn to the illustration, he will find in the right-hand corner a cell that contains something in its interior, at the bottom, something uncommonly like a bacillus. After this

we came to the conclusion that it was impossible to obtain a reliable culture from any commercial source, also that there was a very great danger in injecting into the living animal anything but an absolutely pure culture, and that the only means of obtaining such a thing was to make the culture ourselves ; for such a culture must not only be free from all contamination from bacteria, but also free from any other species of yeast than the particular kind we found best for our experiments, and consequently desired to acquire. It was found that the different yeasts possessed very different properties, possibly antagonistic or inhibitory to one another ; finally, the particular food best suited to any one particular yeast had then to be worked out. The time necessary to settle all these questions took considerably over a year of almost daily experiment, and the uncertainties and disappointments of the earlier experiments can only be imagined. The preparation of an absolutely pure culture was in itself difficult enough, but the preservation of it in a state of absolute purity was even more difficult.

The first step was to obtain, by culture, types of pure yeasts, then to study their respective peculiarities, and finally select that species which was the most active, best in point of size, and otherwise most suitable for the work it was intended that it should perform. The second step was to study the wort or alimentation most favourable to its development, and, lastly, to discover a means of preserving it from all sources of contamination. After a good many considerations respecting the temperature of ascospore formation, the influence of that temperature upon the vitality of various species in the state of cells, the convenience of the preparation of nutritive media and injectable material, etc., considerations, the detail of which seemed at times to draw us too far away, have led us to make choice of the *Saccharomyces cerevisiæ*, a high yeast, as that most fitted for our peculiar therapeutical work.

Having fixed upon our yeast of the future, it behoved us

to ascertain, by successive experiment, the alimentary conditions that were best suited to its development, not only as to its saccharine constituents, but the mineral and nitrogenous constituents as well. Furthermore, the actions of chemical and physical agents, pressure, light, etc., had also to be studied, and it may here be remarked that, unlike bacteria, yeasts do not object to light, and that an alcoholic fermentation will go on better, *cæteris paribus*, in a well-lighted than a dark place. Finally, we had to consider very carefully what fermentable matters should be added to the yeast to act as its food during its sojourn in the body. All this naturally covered a great deal of ground. We shall return to this latter subject anon, and now enter into the relation of how our yeasts are cultivated and prepared for use.

A high yeast mounts to the surface during fermentation, but a low yeast, such as used for lager beer, sinks to the bottom; therefore the first selection was extremely easy. To obtain a pure strain, we made use of Hansen's method, which consists in preparing a malted wort to which had been added 5 per cent. of yeast ashes and 10 per cent. of glycerine. This was placed in a Petri dish, and seeded with the high yeast we had selected. In a short time, little colonies of yeast proceeding from single cells were seen scattered about, and of these a trace was taken up by the platinum loop and examined separately under the microscope. By this means the various less-active and large-sized cells were weeded out, and only the *Saccharomyces cerevisiæ* preserved. It is sometimes very difficult to get a pure strain, and the process has to be repeated from one Petri dish to another—always using the best-looking cells of the previous dish with which to seed its successor—until all the colonies are identical, and until this result is obtained, we do not feel justified in considering that we have obtained a pure strain. A Petri dish is then prepared with a layer of medium very like the former ones, but this time with sufficient gelatine to render it solid; this is

seeded with a pure selected colony, the dish placed in a larger dish containing a neutral gas, and the whole incubated at a temperature of 22° to 25° C.

A wort is now made from malt and glucosides, to which is added a proportion of yeast ashes to provide mineral matter, the whole being diluted according to its richness in albuminoid matter, too great richness being detrimental to a good result. A small flat-bottomed flask is from a half to two-thirds charged with this wort (henceforth to be known as No. 1), and both sterilized in the autoclave. After cooling, the wort is charged with a stream of sterilized air, after which our selected colony is added. Fermentation sets in, the yeast develops well, and, when the fermentation is finished, we find it deposited at the bottom of the flask. The alcoholic fluid is then syphoned off, and the yeast transferred to a similar, but larger, flask prepared in exactly the same manner, and filled rather more than a half with the same wort as the first. During the fermentation, the quantity of yeast increases, which is the reason for using larger flasks, for this process is several times repeated, each time with a larger flask, until we have obtained a considerable quantity and weight of yeasts.

This method of procedure takes a long time, is very tedious, and is somewhat wearisome, as it necessitates so many precautions being taken to avoid contamination by the germs present in the atmosphere; aerial disinfection of the laboratory from time to time is much help in keeping away infection. For greater security we prepare only a small quantity in each series of apparatus, so that, if one goes wrong from any cause, the loss is not so great; nevertheless, the yeasts cultured in this way become decidedly costly. But time, trouble, and money is well expended, for finally we possess a physiological fluid that is completely and without exception innocuous. Having succeeded in obtaining the pure and selected ferments, there still remains to transfer them into an injectable fluid which will be able to retain

them in a state of purity until the moment of their introduction into the system, where it will accompany them for their nutrition. It was evident that, in order to produce the maximum effect at the right time, the yeast must be placed in the best conditions possible for assuring its vitality and preserving the integrity of its functions; therefore it would have to be injected, together with the most appropriate nutriment for its evolution and development. It took a good many experiments before we could settle upon the best formula; but we now have decided upon one which we call No. 2, and generally use with modifications, according to the work that it is expected to do: that is, it varies with the disease which it is sent to attack, phthisis, for instance, requiring much saccharine, cancer next to none, and so on. The wort No. 2 is continually being altered to suit individual cases; latterly I have been adding a certain proportion of artificial nuclein for phthisis cases, and I think with very good results. Before mixing with wort No. 2, the yeasts of the last fermentation are thoroughly oxygenated by a stream being passed through them, so as to provide the cells with a store of oxygen for future use in the system; must No. 2 is then added, and the whole syphoned into a nickel-plated copper apparatus in the form of an inverted cone, the base of which is provided with a bolted cover like that of an autoclave; on its passage into this cone, the mixture is disembarrassed of all the large old and partly inert cells from those that are young and vigorous, which of course considerably diminishes our yield of ferments, but decidedly exalts the physiological efficacy of the fluid. The filtration is effected by the exhaustion of air from the cone, into which the mixture is aspirated through a fine nickel strainer, whose meshes are of such a diameter that it retains all cells whose diameter exceeds 7 μ. This filtrate, when received into the cone, is the mixture we inject, and was jokingly called 'backérine' one day by some friends in De Backer's labora-

tory, and the name was found so convenient that we now habitually use it. A means had to be devised of storing it intact, and in such a state that it could travel without alteration or contamination—in a word, as protected from possible contact with impurities as it had been all through the manufacture. The result of much thought and consequent experiment was a special apparatus which assures an absolute asepsis, and complete freedom from even momentary contact with the air until the needle is thrust through the skin; so absolute an asepsis is not possible with any antitoxin syringe. The apparatus consists of an aseptic tube or cartouche which holds the fluid, and a special syringe to hold it. The cartouche is a small tube of glass (made without lead), with an external diameter of $\frac{3}{8}$ inch and a length of $1\frac{3}{4}$ inches to a part which is drawn out into a fine tube about 2 inches long; into the large end is fitted a tight plug of caoutchouc specially prepared without any noxious mineral, and which contracts in the boiling water of sterilization, but expands when cold. The cartouche is sterilized, the plug being pushed home to the bottom at the narrow end; the tubes are again sterilized immediately before being filled. This process is as follows: The fluid in the metal cone is charged with air sterilized in a special way to a pressure of six atmospheres, and is conducted through a system of tubes and taps to an outlet into which fits the narrow end of the cartouche; the tap is turned, when, by means of the pressure behind, the backérine enters the cartouche and pushes the plug in front of it, the plug being restrained from being driven out by the pressure of the thumb; the tap is turned off, and the narrow end of the tube immediately sealed in a blowpipe flame; the tube now contains $1\frac{1}{2}$ cubic centimetres of backérine hermetically sealed. When the tubes have to travel, it is desirable to protect the plug by a wad of cotton-wool and a dab of sealing-wax; but they do not travel well, especially in hot

weather. The cartouche is now ready, and is preserved in cases or boxes stored in a cool place. The ferments are seen within the tube at the bottom, of a pale fawn colour, the liquid being quite clear.

Under these conditions of pressure and exclusion from the air, the yeasts will not ferment, or, should they do so slightly, the disengagement of carbonic acid gas increases the pressure within the tube, and so arrests further fermentation, obliging the ferment to live in a state of latent activity. If the narrow part is broken or cracked, fermentation sets in briskly almost at once; very hot weather will also cause fermentation in the tubes, and those whose plugs are the least tight (owing to unevenness in the calibre of the tube) may have them blown out.

The special syringe consists of a hollow cylinder of nickelled copper, fenestrated with two long slots opposite to each other; both extremities are wormed; on to the lower is screwed a little spherical cap terminating in a narrow male-wormed cylinder for the reception of the shoulder-piece of the hypodermic needle. At the upper end of the cylinder is screwed a hollow disc perforated with a hole, through which passes a metal rod, on to the lower end of which a small metal disc is soldered, and the top end furnished with a screw-head; this rod is used as a piston to push down the plug of the cartouche when prepared for use.

The mode of using this apparatus is by first removing the sealing-wax and cotton-wool from the cartouche, the contents of which are rendered homogeneous and equally cloudy by shaking, or by holding the tube between the fingers and thumbs, as in making a cigarette, and rolling it from side to side. The head of the syringe is unscrewed and the cartouche slipped in, so that the narrow part projects through the lower end of the syringe, but prevented from actual contact by a small piece of drainage-tube; the head of the syringe is replaced so that the cartouche is solidly fixed between the

drainage-tube round its narrow end and a disc of rubber which lines the metal cap of the head. The metal disc of the piston-rod will now be found to rest on the rubber plug of the cartouche, which should be next grasped between the fingers and thumb of the left hand through the fenestrations, pressure being exercised so as to extrude the narrow part as far as possible; this is filed with two or three strokes of the file provided in the case, and the protruding end snapped off. The filing should be done as close to the syringe as possible, the object of pressing the cartouche down being to obviate the chance of any projection of glass beyond the syringe after the lower end of the cartouche is removed. All that remains to be done is to screw on the previously sterilized needle, and the apparatus is ready for use. In order to ascertain the amount of force necessary to push down the plug, the syringe should be held with the first and second fingers round the crooks, and the concave top of the piston-rod resting on the ball of the thumb; the point of the needle should be directed upwards; a squeezing movement will now cause the fluid to flow from the needle and trickle down it: this aids in sterilization.

The skin or subjacent muscle should be quickly pierced and the plug pushed down, not too quickly; the amount requisite having been injected, the needle is rapidly withdrawn, and the spot gently massaged to aid absorption. The needle is unscrewed, sterilized, and put away with its wire in the case; the best means of sterilization is by dropping into alcohol. The cartouche is removed and thrown away—we never use them a second time—but the syringe is always ready, as there is nothing to get out of order; it can be entirely taken to pieces, and is easily sterilized—indeed, it never gets contaminated, for the needle is the only part that ever comes in contact with the fluid used for the injection.

By the employment of such a cartouche we gain the advantage of having the remedy always ready for use without any further preparation; the necessity also is obviated of trans-

ferring the fluid to be injected into a recipient, and from this to a syringe, all being exposed to the bacteria-laden air during the manipulation, as well as exposed to other sources of infection, unless tedious and cumbersome processes of sterilization and asepsis are carried out, the details of which are practically impossible, clinically, in ordinary general practice. We consider this aseptic cartouche to be more economical, portable, more simple, and, above all, more sure, than any other means of administering subcutaneous injections yet devised ; it could be equally well used for storing and preserving antitoxins.

In the above chapter I have described the syringe which has been made for me by Messrs. Maw, Son and Thompson. It differs very slightly from that of De Backer, but I think is more handy.

CHAPTER VI.

THE ACTION OF PURE FERMENTS WITHIN THE HEALTHY ANIMAL SYSTEM.

Being now acquainted with the action manifested by bacteria against yeasts and the reciprocal antagonistic action of yeasts upon bacteria of all sorts, it seemed to De Backer that, before advancing to the study of the influence that yeasts might have upon bacteria exercising their functions within an animal system, it would be more correct to ascertain by experiment what the effect of pure ferments would be upon the healthy organism, also the influence that healthy organs would exercise upon these internal therapeutic agents; that is to say, what would be the phenomena produced by the introduction of pure ferments into the living system, as far as possible known to be in a state of health. The following experiments were carried out by De Backer and Bruhat.

Experiment I.

On May 3rd, 1893, a male guinea-pig, a year old, weighing 830 grammes, and in a good state of health, was taken for the first series of experiments. The carotid artery was first laid bare and quickly severed, the blood being received into a sterilized Petri dish, and immediately mingled with an equal volume of backérine. The whole was introduced into a sterilized tube, which was straightway plugged with sterilized

cotton-wool. This was about one o'clock in the afternoon, the temperature of the laboratory being 26° C. The blood and various organs were examined as under:

I. *Arterial Blood.*—At six o'clock in the evening fermentation showed itself very decidedly. The next day it was practically over, and the frothy head subsided. There was a fresh, sweet, alcoholic, somewhat aromatic odour; the liquid, of a pale rosin tint, held in suspension some blackish clots of fibrin and red corpuscles. The mixture was shaken up, and three cover-glass preparations made from it, one stained with fuchsine, the second with methyl violet, the third unstained; all were fixed with Canada balsam. No blood cells were seen under the microscope, though there were a large number of yeast cells, perfectly stained, many of them being in a state of gemmation. The conclusion was that the presence of arterial blood drawn from the living animal did not prevent and hardly retarded the fermentation of backérine. On May 25th the liquid had become pale gray, with brownish black clots deposited at the bottom of the flask. The whole was shaken up, and the mixture again examined. Many perfect yeast cells were seen, apparently still living, but to make sure some of the liquid was mingled with a little honey, when fermentation commenced anew. The blood, therefore, had not putrefied after an interval of twenty days. On June 14th the flask was again examined; it contained a pale yellow fluid, with a gray brown coagulum, with some black bits in it at the bottom of the flask. The odour was still that of alcohol, with a peculiarity that might have been due to the production of ethylacetic ether. Under the microscope the cells appeared to be well preserved, readily taking the stain. A few cocci, and one or two bacteria, were seen in the liquid, and later on some were seen inglobed in the yeast cells, especially cocci.

II. *Venous Blood.*—An hour after the death of the animal the heart was removed, and was found to contain a black

coagulum of blood; this was mixed with half its volume of backérine, and the mixture diluted with a little distilled water. At 6 p.m. fermentation had not yet commenced. The next day, however, it was found to be ended, and the froth all gone down, yet a slight shaking disengaged numerous bubbles of carbonic acid. The fluid was much darker than the other, but possessed the same alcoholic and aromatic odour. Under the microscope a number of yeast cells were seen in process of gemmation. On May 26th the mixture appeared a creamy-brown mass, still with the alcoholic odour; under the microscope the yeast cells appeared healthy. The flask was then left to itself, the plug of cotton-wool removed, and a simple paper cap substituted. On June 14th the flask was again examined; on the surface was spread a white fungoid layer, covering a creamy-brown magma of the consistence of honey, the odour still being alcoholic and aromatic. The white layer on the surface was found to consist of yeast cells in the hyphomycetic shape, though some were seen in the ordinary form of conidia. The brown magma also contained conidia, with some crenellated and fibrinous flecks.

III. *Lungs.*—A portion of the fresh lung was cut out, macerated in a little distilled water, and introduced into a flask with some backérine. At six o'clock no fermentation had begun, but the next day it was very active; small fragments of lung were floating about on the surface in the form of small brown and gray flecks. The liquid containing the ferments was whitish, and the odour of alcohol very distinct. On May 26th there was no change in the mixture, the odour of the alcohol being still present. This flask was then left to itself, being simply covered with a paper cap. On June 14th the gray lung substance had sunk in the flask instead of floating, and rested on the top of a layer of yeast cells, which formed a white mass. The microscope showed yeast cells in good condition, some cocci and bacilli, several of the latter

being inglobed by the yeast cells; of the cocci very few were inglobed in comparison to the bacilli.

IV. *Liver.*—A piece of liver was cut out, macerated in distilled water, and backérine added. The next day the flask contained a brown liquid, still allowing some bubbles of gas to escape. The odour of alcohol was quite fresh, and the yeast cells appeared healthy.

It would be tedious to recount seriatim the remainder of the experiments on this head;* suffice it to say that the brain, muscles, testes, vasa deferentia, and gall-bladder were all subjected to the same process, and were examined at the same intervals of time, the results being very much the same as those above mentioned. The following conclusions seemed justified: That the presence of organic matter in no respect hindered the physiological functions of the yeasts; that the alcohol and other products, formed from the saccharine matters, prevented any putrefaction of the organic matter; that later on, when exposure to the air had generated secondary fermentations, and thereby provided a medium of culture favourable to the development of the acetic and butyric vibrios, and micrococci too, both the latter were inglobed by the living saccharomycetes; but this did not occur when these were dead or degenerating at the time that the bacteria were developing; finally, that micrococci seemed to be more easily inglobed than bacilli. Having ascertained this much, the next experiment was naturally devised in order to ascertain the effect produced by yeasts when introduced in the form of backérine, no longer in the presence of healthy though dead organs, but in the presence of healthy organs in the living system; to find out, if possible, whether they would be able to there exert their physiological functions and produce an alcoholic fermentation.

* For a detailed account see 'Les Ferments Therapeutiques,' by Dr. de Backer.

Experiment II.

In order to prove the presence or absence of alcohol in this experiment, both in the backérine to be injected and in the animal itself, two very distinct tests were made use of, that of the action of alcohol upon carbonate of potash and iodine (the reaction giving the characteristic odour of iodoform), and that of alcohol upon chromo-sulphuric acid, obtained by dissolving crystallized chromic acid in strong sulphuric acid, specific gravity 1840 (the reaction being the reduction of the chromic acid, and the formation of the green sulphate of the sesquioxide of chromium). The proof was first applied to the backérine, so a small quantity of the injectable fluid (wort No. 2, *vide* p. 93) to be used was filtered, and boiled with iodine and potass carbonate in slight excess. Not the slightest odour of iodoform could be detected, thus proving the absence of alcohol.

In order to test the products of expiration of an animal, it was introduced into a tightly-closed box, through which a current of air was made to pass. Two double bulbous tubes containing the chromo-sulphuric acid were fixed, one at the entrance, and the other at the exit of the air current, in such a manner that the air was obliged to pass through the reagent. The little animal was subjected to a preliminary experiment without any injection having been administered, in order to ascertain if alcohol was normally excreted from it or not ; it was kept in the box for twenty-four hours without food. At the end of this time the reagents in both bulbs still retained their original orange-red colour, thus proving that alcohol was not normally excreted from the animal by skin or lungs, nor did the fumes arising from any excretions give rise to any alcoholic reaction. The same animal was then injected with 1 c.c. of backérine and replaced in the apparatus, still without food. After a time the fluid in the tube of exit began to change colour, first to a russet, then from a brown-

green to a bottle-green, finally to an olive-green. The reagent in the tube of entrance still retained its original orange-red colour. Sometimes as much as eight, ten, or even twelve, hours are necessary to get a decided reaction. This can be easily understood if we bear in mind what a very small quantity of alcohol could be produced altogether within the system of the animal, and what a still smaller proportion would be eliminated in the air expired by it. Yet, small as the quantity may have been, the reaction was evident, alcohol being the only substance known that can cause this change of colour.

Experiment III.

Objections having been raised that two different tests were applied for the detection of alcohol, one to the injectable fluid, and the other to the products expired by the animal, it was decided to apply the same test to each, the chromo-sulphuric acid test being the one chosen. This necessitated the construction of a special apparatus. Two large flat-bottomed flasks were plugged at the neck with indiarubber, perforated with two holes; through one passed a glass tube, the end of which nearly touched the bottom, the other end was provided with bulbs, arranged in such a fashion that there could be no bubbling over; by this tube the entrance of air into the flask was to be effected. Through the other hole in the plug passed a similar tube, but the part within the flask was much shorter, not passing farther than the neck. It was by this tube that the air would find an exit after having bubbled through the fluid in the flask; the outside end of this tube, also provided with bulbs, was connected to an aspirator or suction apparatus, which exhausted the air, thereby causing a current that could be regulated at will. One of these apparatus contained the injectable fluid (wort No. 2) without the admixture of yeasts, both fluid and vessels having been previously sterilized. The second apparatus, also sterilized, contained

the pure yeasts, which had been previously well washed with sterilized distilled water until no trace of sugar, etc., remained; they were then suspended simply in sterilized distilled water. Air was now sent through the fluid in each apparatus for twenty-four hours, at the end of which time it was found that each bulb still retained its orange-red colour, so that it was evident that no alcohol was present in either the yeasts or the fluid to be injected.

The third apparatus was designed for the purpose of ascertaining the presence of alcohol in the air expired by the animal injected. It varied a little from the apparatus first made use of for the same purpose in some details; it was larger, for one thing, so that it could contain three or four guinea-pigs, or even five small ones; and, for another, it was arranged so that the air inside could be regulated and maintained at any temperature that was desired. The same preliminary experiment was made with the uninjected animal as in the former experiment, with the same results, that no alcohol could be detected. Then an injection of backérine was administered into the subcutaneous tissue of the test animals, the point of inoculation being sealed by touching it with a hot wire. One c.c. of equal parts of the yeast and the wort (already proved free from alcohol) were used for each injection. The guinea-pigs were placed in the apparatus, which was hermetically sealed, with the exception of the entrance and exit of air. The reaction of alcohol showed itself much more quickly now that a number of animals were under experiment, besides another favourable circumstance, in that the temperature could be raised and maintained at 30° C. In some of the experiments the reaction appeared in two hours; the reaction invariably showed the characteristic green colour in the bulb of exit, the bulb of entrance still maintaining its original golden-orange colour.

We may remark that the little animals did not appear to be at all upset, either by the injection or their in-

carceration, as long as the current of air was sufficiently rapid.

It may be urged that the reaction may not have been caused by alcohol at all, but by something else; but, in answer to this, we can only say that none of us are acquainted with any substance but alcohol which is capable of giving this reaction; it seemed evident also that alcohol could not have effected entry, and must therefore have been generated in the apparatus.

The conclusions drawn from these experiments were: That, normally, neither the products of expiration nor the fumes of the secretions or excretions of animals cause any such reaction; that the ammonia or ammoniacal salts could only neutralize a very small portion of the sulphuric acid, but would not affect the chromium compound in the slightest degree; besides, in the preliminary experiment nothing like it was produced. It may fairly be asked: Why, then, should an injection of mingled saccharine and yeast set up such a change?—especially since it had been shown that the air, which bubbled through the saccharine and the yeast respectively, did not decompose the chromo-sulphuric acid, thereby proving the absence of alcohol in both constituents of the backérine.

Alcohol is the only known substance which can produce such a reaction upon chromo-sulphuric acid; and although this particular apparatus was devised by Messrs. de Backer and Bruhat, the test itself has been known for a long time, and has been considered so precise and sure that, besides the iodoform test, it is the only one employed in French medical jurisprudence for the detection of alcohol; it is also recommended by English authors on the same subject, Taylor amongst them.

The same test was used by Messrs. Lallemand, Perrin and Duroy, to demonstrate that alcohol administered by the mouth could be excreted by the skin and lungs; an Italian

greyhound was selected, as that breed of dog possesses a very fine skin with but little hair.

Other experiments were made by injecting the yeasts, washed until the filtrate showed no signs of alcohol, separately from the injectable fluid; the green reaction was produced. Sometimes, with yeast alone, after a long time and when conditions were favourable, a feeble reaction was obtained.

After these various experiments were finished, the conclusions that seemed justified were that young and pure yeast cells injected with aseptic precautions into the economy, together with the nutritive and fermentable matters necessary to them, not only survived the injection, but were capable of exercising their normal functions in reducing the saccharine elements injected with them. No doubt the other products of fermentation, carbonic acid, succinic acid, etc., were also formed, besides the alcohol whose presence had been proved, but the means of actually proving this were not easy to devise, neither does the proof seem very necessary.

Another series of experiments was now instituted in order to ascertain the peculiarities of the diffusion of the yeast cells within the system.

Experiment I.

Ten c.c. of backérine were injected into the subcutaneous tissue of a male guinea-pig, with the usual antiseptic precautions; twenty-four hours afterwards a few drops of lukewarm distilled and sterilized water, slightly tinged with methyl violet, were placed in a Pravaz syringe, the needle of which was inserted into the same place as the injection of the previous day. Aspiration was then effected from within outwards; a few drops of liquid were thus withdrawn, which were examined under the microscope. Some epithelial cells were seen, a large number of both mononucleated and polynucleated white corpuscles, which varied in shape and changed

in form whilst under observation ; a few healthy-looking yeast cells were also seen, but no red corpuscles.

This experiment was repeated several times, with a longer interval from the time of injection. Forty-eight hours afterwards the same elements were observed as in the preceding case, but the yeast cells were fewer in number, and some of them had taken on degeneration forms (hyphomycetic), probably due to the fact that the saccharine injected with them had been entirely exhausted and reduced. In many of the slide preparations yeast cells were seen to be inglobed within the leucocytes, especially the mononuclear leucocytes, which was a very interesting fact from the clinical point of view, inasmuch as it gave some idea as to how long the efficacy of each injection into the system was likely to last, and how long it would probably be before the yeast cells would lose their functional power within the economy. It also showed in what manner the yeast cells would be finally removed from the body when their work was accomplished. My own observations made upon a series of cases of tuberculosis tell me that in the diseased system the yeast cells maintain their vitality and functions for a very much longer time than in the healthy system ; that successive broods of yeasts are formed within the economy, as evidenced by secondary, or even tertiary, reactions ; and, finally, that the leucocytes do not devour and get rid of the yeast cells as long as they are aiding the former in their legitimate work.

During one of these experiments, the guinea-pig, which had been only loosely fastened, gave a jump at the moment of inoculation, thereby causing the needle to penetrate the thorax, which received the injection. A little while afterwards blood appeared at the point of puncture. A few drops were secured and microscopic slides prepared from them, which were then examined. A large number of red corpuscles were seen, together with a much larger proportion of white corpuscles than the normal, also numerous yeast cells, many

more, indeed, than were found at the point of inoculation in the former experiment (p. 107). According to the results of these observations, a new series of experiments was instituted for the purpose of ascertaining the course and effect of yeast cells, with their necessary nutriment, when directly injected into the blood-current in different regions.

Experiment II.

Into the large vein of a guinea-pig's ear, about 5 c.c. of backérine were injected in different portions at various intervals, extending over ten hours. The next day the other ear of the animal, after a thorough washing and asepsis, the final washing being done with æther, was punctured in the vein with a lancet, a few drops of blood extracted, slightly stained with violet, and examined. Some of the preparations contained no yeast cells, but in others a few were discovered. This experiment was repeated several times with the same result, but as these experiments had been conducted in the same laboratory in which continual experiments with yeasts had been going on for over a year, it might have so happened that yeast cells might have been conveyed to the slide preparations from outside, on glass slides, dusters, or even the hairs of the animal itself. Microscopic examination of the dust of the laboratory showed this to have been quite possible ; therefore, to avoid all such contamination, two guinea-pigs were procured and kept for some days away from the laboratory at a private house ; new slides and cover-glasses were obtained as well as dusters that had never yet been used. The guinea-pigs were kept apart and inoculated with backérine separately, the point of insertion of the needle being immediately closed by a scar made by the point of a hot iron. Here, then, there could be no possible contamination from outside yeast cells, yet the results of the experiments were exactly the same. In some of these experiments the blood was examined before inoculation as well as after, when it was

found that in the latter case a much larger proportion of white cells was present, causing a decided leucocytosis.

Experiment III.

A rabbit was injected with 10 c c. of backérine into the subcutaneous tissue of the left thoracic region, also in the corresponding region on the right side, the points of both inoculations being closed with the hot wire, but before this was done a little of the fluid was squeezed out, showing no trace of blood, thereby proving that the fluid had been injected into the subcutaneous tissue, and not into any blood-vessel. The next day a prick was made with all aseptic precautions into the vein of the left ear, and a few drops of blood removed with a sterilized pipette. A series of cover-glass preparations were made, all being stained with a cold solution of violet. Many leucocytes were seen in all the preparations, and in a great many sometimes one or two, or even three, saccharomyces cells.

Experiment IV.

During a period extending over ten hours a guinea-pig was given four injections each of 10 c.c. of backérine into the subcutaneous tissue of the abdomen ; the creature was left alone until the next day, when it was taken to the laboratory and killed. In order to preserve the vascular system intact, the animal was killed by strangulation ; it was then opened, and a certain number of preparations made from the blood and other humours. It must be understood once for all that in every experiment all instruments, glass rods, vessels, ligatures, operator's hands, etc., were always rendered as carefully aseptic as is done in abdominal operations on the human body, hence it will not be necessary to keep repeating the fact of sterilization. The regions from which the preparations were taken, with the results observed, are as follows :

I. The fluid or lymph of the subcutaneous tissue adjacent

to the point of insertion : The result showed numerous epithelial cells, a fair number of leucocytes, and some healthy-looking yeast cells.

II. Lymph taken from the inner surface of the pleura, a region distant from the place of inoculation and separated from it by the diaphragm : The result showed epithelial cells, but neither leucocytes, red blood corpuscles nor yeast cells.

III. Vein of the skin near the spot of inoculation : The blood appeared normal with the exception of a large proportion of leucocytes ; also yeast cells were discovered in the ordinary form of conidia.

IV. Superior mesenteric vein : Many leucocytes and yeast cells were noticed.

V. Jugular vein : Many preparations gave no result ; only two showed any yeast cells, but these were very distinct and presented the form of ascomycetes. These were not confounded with mononucleated leucocytes, as these latter stained a blue tint and were filled with granulations, whilst the yeast cells had their protoplasm clear, and contained from one to five endogenous spores of a deep violet hue.

VI. Liver : A piece was taken, chopped up and macerated in water ; the resulting liquid was examined : many pigmented cells were seen, red and white blood corpuscles, also a few yeast cells, but not many.

VII. Pulmonary vein : Yeast cells were seen in the ascomycetic form, but two cells were attached as links of a chain (hyphomycetic form), very like those noticed in the subcutaneous tissue forty-eight hours after injection (*vide* p. 107). This is the form that yeasts adopt when in films on the surface ; that is to say, when exposed to the air and leading an aerobic existence.

VIII. Heart : The blood in the heart was found clotted ; these clots were removed and examined ; the serum expressed from the clots contained no yeast cells, but the fibrinous mass which formed the bulk of the clot enclosed some yeast cells,

both conidia and ascomycetes, as well as red and numerous white corpuscles.

IX. Muscles: One of the muscles of the thigh was dissected out and washed, then sliced in its long axis. The central part thus laid bare was then touched with a glass rod, and the result spread on a cover-glass, with a little sterilized distilled water. Fine separated muscle fibrillæ were seen, with saccharomyces cells in the form of conidia.

The conclusions drawn from this series of experiments were that young and pure yeast cells, when introduced into the animal economy through the veins, enter into the circulatory current, survive in it, and are capable of exercising their functions within it (Experiment II.); that this also obtains when backérine is injected subcutaneously, without any direct communication with the bloodvessels (Experiment III.); that the laws of diffusion appeared to be (Experiment IV.) that

1. The saccharomyces cells diffuse themselves with great rapidity in the tissues adjacent to the place of insertion, mingling with the fluids which these tissues contain, and penetrate by this means both the muscular tissue, organs, and blood-current.

2. The nearer the organs are to the spot of inoculation, the greater is the number of saccharomyces found within them. This is important clinically in guiding us to choose the best places for administration in different diseases.

The other phenomena noted were: That in addition to the action of the invertin and diastases secreted by the yeasts; in addition to the production of alcohol, etc., caused by their action upon the fermentable matter of the backérine; in addition also to their phagocytic power, the yeast cells set up an increase of circulation and abundant leucocytosis. Finally, that the vitality of the yeast cells within the *healthy* system is not indefinite, lasting perhaps some four or five days; but the actual time appears to be in relation to the quantity of fermentable matter injected with them, or that they can find

within the system into which they have been thrown. After having played their part, their functions being ended, the cells degenerate, and become the prey of the macrophages, which digest them, as can be easily understood when we remember that a considerable leucocytosis is provoked. This inglobing of the degenerating yeast cells may be very well studied under the microscope by using some blood from the tail of a newt, as recommended by Schäfer.*

The above remarks apply only to the duration of vitality of the yeast cells within the system of the healthy guinea-pig. In the human being, especially in cases of individuals containing much glycogen and in those suffering from diabetes, saccharomyces cells have been discovered in the blood even three months after injection.

It may reasonably be asked, How can saccharomyces cells (which ordinarily prefer an acid, or slightly acid, medium) exist and develop in the alkaline fluids of the body, which, with the exception of the arterial blood, possess no oxygen? Now, the experiments detailed in this chapter show that they certainly do exist, have their being, and exercise their functions therein; therefore an answer to the question certainly exists, and may be found in the fact that, although old and inactive yeast cells *cannot* exist in such a condition, yet those which are young and vigorous are able to do so, especially after they have previously undergone the process of oxygenation, as described in a previous chapter. The absence of *free* oxygen is no bar to fermentation, for Pasteur has declared fermentation to be the consequence of anaerobic life.

As regards alkalinity, I quote an experiment to show that a slightly alkaline medium is no great hindrance. I caused some of our usual cartouches to be charged with pure ferments and backérine fluid, rendered slightly alkaline by phosphate of soda. This was in the middle of June, and so they remained for three months, until, in the middle of September, I released

* 'Essentials of Histology,' p. 21.

the contents, which were mingled with the sputum from a phthisical patient. The fermentation was active and decided. On examination, the phagocytic power of the yeast cells was well displayed over the different kinds of cocci in the sputum. No inglobement of any tubercle bacillus was noted ; but this is not surprising, as I could only find one such bacillus after hunting through several preparations. This patient had been for five months under the ferment treatment, previous to which his sputum had been loaded with tubercle bacilli. On the question of alkalinity, a quotation from Dumas would not be amiss : 'Small quantities of free bases possess no marked influence over the phenomena of fermentation ; yet, and the same applies to acidity also, a *too* alkaline medium hinders and prevents fermentation.' Now, the human blood does not possess this extreme alkalinity, but it will be interesting to ascertain by subsequent experiment what the effect will be upon rats, whose blood is excessively alkaline.

It has been shown that yeasts can retain their functions when exposed to much, to little, or to no contact with air (provided that in the latter case the cells have been previously aerated, as Bourquelot remarked) ; but certain alterations of function occur under these different conditions—alterations of cell growth, production of alcohol, etc. Dumas has furthermore demonstrated that yeast cells retain their activity when preserved in many different gases besides oxygen, such as hydrogen, nitrogen, carbonic acid, nitrous oxide, carburetted hydrogen, etc. Reference is here made to Experiment IV. of this series, p. 107, during which two cells of the hyphomycetic shape were seen in the blood from the pulmonary vein—a form in which they certainly were not when injected. Now, this shape is seen in Nature, as aforesaid, on the surface of fermenting liquids, forming the film, when the sugar is almost exhausted, and the cells are in contact with the air. In the case of the pulmonary vein we have exactly the same conditions, for at that time the saccharine in the backérine was

becoming exhausted, and the yeast cells had been exposed to the oxygen in the capillaries of the lungs, a further proof that yeast cells enjoy their normal existence when present in the blood.

As to the effects of the pressure that the yeast cells might be called upon to undergo within the body, the reader who cares to pursue this subject further is referred to the communication made to the Royal Academy of Belgium by Messrs. A. Certes and Denys Cochin on the effect of high pressures upon the vitality of yeast cells. It will be sufficient here to say that the yeast cells are preserved with their fermentable matter in the cartouche, under a pressure of six atmospheres, and that in this state they retain their properties for months.

The harmlessness of injections of pure yeasts into animals has been distinctly proved. After ascertaining that the yeast cells could live and cause fermentation in the animal economy, it was desirable to find out whether such injections could produce any harmful or deleterious result to the animals subjected to them. The experiments of Dr. Capitan and of Dr. Maryx showed that enormous quantities of yeasts could be exceedingly well borne by animals ; that the yeast cells were afterwards found abundantly in the blood, and later in the urine. Albuminuria was sometimes noticed by the former experimenter, but only twice by the latter, partly, perhaps, because he did not use such large quantities, Dr. Capitan having administered to a dog as much as 4 grammes of yeast in 60 c.c. of water. For human beings we do not use anything like these doses, so that albuminuria need not enter into our calculations.

A considerable number of guinea-pigs were injected in Dr. de Backer's laboratory during the course of these experiments. The pure cultures of *Saccharomyces cerevisiæ* were injected into various places and organs, including the muscular tissue, peritoneum, and lungs. Some were injected daily with several cubic centimetres for periods extending over months, all being

well borne, so much so that some of the little creatures got quite fat. In one case, a female guinea-pig, a year old, and weighing 750 grammes at the commencement of the experiment, received a daily injection for forty consecutive days. She kept well and had good appetite all along. At the end of the course her weight was found to have increased to 897 grammes. A rabbit treated in the same way gave similar results.

After being thoroughly assured of the innocuity of the method practised, and of the materials used, under the conditions imposed, De Backer and Bruhat desired to watch the effects of similar experiments upon the human body. M. Bruhat offered himself as the subject. He is a man of average height, good physique, though spare; dark-complexioned, with bright black eyes; energetic, eager and alert; one is struck with the intensity which he throws into any work done or into any subject of conversation. It was, then, on such a nature and constitution that the backérine was to be tried. An injection of 6 c.c. of backérine was administered subcutaneously into the lower region of the abdomen on the right side at 10.30 a.m. What follows shall be related in his own words:

'The injection was not painful: three or four minutes afterwards I perceived only a slight feeling of smarting.

'12 *o'clock*.—Lunched with good appetite (roast meat, also farinaceous and saccharine food, with white wine). Towards the end of the meal I began to feel a little inflammation and tenderness to the touch at the place of inoculation, but there was no redness of the skin; the large subcutaneous vein of the abdomen (superficial epigastric), near which the needle had been inserted, was rather prominent. The slight pain felt was merely local; there was none elsewhere.

'1.30 *to* 3.30 *p.m.*—I was out driving; nothing much was noticed except a slight discomfort on getting in and out of the carriage.

'4 *p.m.*—The whole of the right inguinal region was tender to the touch; the skin seemed rather stretched, but the vein was no longer prominent. Frictions of warm camphorated camomile-oil were used to soften the distended tissues.

'4.30 *to* 5 *p.m.*—My head felt rather heavy, and I had a great tendency to sleep. There was no shivering nor fever, but I had a slight sensation of cold, and my hands were cold, although I was quite near the fire. I then walked to Dr. de Backer's, Rue Chausée d'Antin, whom I found with one of his colleagues. Conversation quickly dispelled the disposition to sleep. I remained there till seven o'clock, experiencing nothing but a little pain and discomfort in getting up or sitting down.

'7 *p.m.*—Dinner; excellent appetite. Food much the same as at lunch. During the day there had been neither diarrhœa nor constipation, but a slight anuria; only one slight passing of urine since the injection.

'8 p.m. to midnight nothing fresh was noted. On my return to the Rue de Berlin'—where M. Bruhat was then living—'the pain was so slight that I did not trouble to rub the spot of inoculation with the camomile-oil. I soon went to sleep, but awoke at 2.30 a.m., the reactional crisis then taking place. There was very little fever, but the skin over the whole body was dry and burning, the mouth also dry and the tongue white; however, there was very little rise of temperature. The sensation then experienced was very queer; it seemed as if, between the peritoneum and the skin of the abdomen, particularly on the right side, there had been placed a somewhat heavy leaden casing, which compressed it. Next followed a rather sharp pain in the back, which quickly became general, and was accompanied by a marked sensation, not exactly of formication, but as of worms crawling very slowly, this sensation being felt all over the body, even in the hands and feet. This condition, during which I could not sleep, lasted until half-past five in the morning, when the

sensation rapidly abated, and I could turn in bed, bend and stretch my limbs without pain ; but the place of injection was still tender to the touch.

'It appeared to me just at that moment that my body resembled a very full wine-skin, in which all the elements were in a state of plethora, and that I completely filled every crevice of my *ego*. The impression produced was very curious, with an indefinable sensation of well-being ; after that I soon went off to sleep again, to wake at 7.30 in a colliquative perspiration.

'At 10 a.m. there no longer remained any trace of pain, even on movement, except that the spot of insertion was still tender to the touch. The whole right lower abdominal region was red, and a very decided lymphangitis existed there. By midday the local condition had improved more and more, but the anuria still persisted. I partook of lunch with white wine as usual, with good appetite. The local state improved during the afternoon, the spot of injection being hardly painful to the touch, with the exception of a small point of induration about 4 centimetres around the puncture ; but the glands of the groin were much swollen, and of the size of a hen's egg. The redness of the skin had much diminished.

'At 5 p.m. I partook of a couple of glasses of beer, which were followed by an emission of urine.

'7 *o'clock*.—Dined with excellent appetite ; beer, and afterwards coffee, were partaken of in the way of fluids. The anuria still persisted.

'At 11 p.m. the adenitis appeared to be resolving, and the swollen glands much less painful to the touch. On the other hand, the spot of insertion on the right side had become more tender, and frictions with camomile-oil were used.

'A very quiet night was passed, with uninterrupted sleep. On awaking there was no longer any redness of the skin over the abdomen, the gland was scarcely the size of a hazel nut, and hardly painful at all, even to the touch. The spot of

insertion was still a little inflamed, but much less tender than the day before. The anuria, which had persisted since the injection, had now ceased. The urine, on analysis, showed neither sugar nor albumin, but—a phenomenon worth remembering—a few inappreciable traces of phosphates.

'At mid-day the appetite at lunch was excellent. By midnight the adenitis had nearly all gone; the slight inflammation at the point of inoculation alone persisted. The night, like the preceding one, was quite calm. In the morning the anuria had entirely disappeared, the glandular swelling had gone, and the tender spot of insertion felt nearly well, even on handling. In the evening the local condition was still better, and the next day, that is to say, about ninety hours after the injection, all inflammatory phenomena had ceased, and the system returned to its normal state.'

We see from this experiment that the reaction within the system was of a certain intensity; that the injection of backérine in a healthy subject produces no lasting unpleasant phenomena, and that the experimental leucocytosis thus produced does not compromise the health of the person experimented upon.

The reader may have noticed the constant repetition of 'excellent appetite.' Now, this excitation of appetite is a constant fact that we notice after injections of backérine into both healthy and diseased animals, many of them running to their food soon after their release, often eating greedily. Now, this was never seen when animals were inoculated with pathogenic substances. I have frequently remarked this phenomenon in my patients who are undergoing this treatment, especially in phthisical cases, which is the more remarkable and satisfactory, as it is in them that we so often find degeneration of the digestive powers, with feeble and capricious appetite, accompanied so often by vomiting and nausea.

CHAPTER VII.

ACTION AND THERAPEUTICS OF PURE YEAST FERMENTS AND THEIR PRODUCTS.

From the study of the various scientific phenomena *in vitro*, the work has been carried through experiments on the healthy animal economy to the final stage of the whole subject, which is the action of these pure yeast ferments upon the diseased system, the study of the special diseases in which they are likely to be efficacious, their mode of application, the choice of locality selected for their injection, and the reactions produced, after which we shall close the chapter with a few clinical hints and instructions.

The great principle underlying the whole of the treatment by pure ferments is the substitution of a natural, healthy, alexinic fermentation for one that is pathological and destructive. We have seen in a previous chapter the great help that can be obtained from phagocytosis alone, that the injection of these auxiliaries is perfectly innocuous, and in no way embarrasses the animal system. Let us now turn to the physiological action and therapeutics of the products of yeast cells, alcohol, carbonic acid, glycerine and succinic acid, and see what part they may be likely to play in this new treatment. It must be borne in mind that although these substances are necessarily produced in small quantities, yet they are produced in the place where they have immediate scope for

the exercise of their greatest power at a time of their maximum activity, which is the nascent state.

Carbonic Acid.—The ingestion of this substance exerts a calmative action over the stomach, therefore allaying vomiting; it is also a diuretic. It has been used, on account of its soothing action, to allay the pain of cancerous ulcers and gangrenous wounds. To a certain extent it is antiseptic, lessening suppuration, and promoting the healing of wounds. It is exceedingly useful also in counteracting a phosphatic diathesis. When injected hypodermically, it promotes the union of divided tendons. Probably its greatest use in the ferment treatment is its diuretic action, by which much of the toxins of bacteria are eliminated, but in diabetes it may have some direct action on sugar formation.

Alcohol, when ingested, stimulates the glands of the stomach, and aids digestion, especially in the old or those feeble from disease. It is readily absorbed by the blood-vessels, less so by the lacteals. It stimulates the heart and accelerates the pulse, but in fever, where the pulse rate is already high, alcohol acts by lowering it, the heart is steadied, and, from its systole and diastole being more perfectly performed, more blood is caused to flow at each beat. Alcohol also stimulates the nervous system, sometimes to the extent of enabling it to resist and ward off attacks, or at least gain time for the system to rally its forces.

These actions are seen following its administration at the commencement of a catarrh, of a paroxysm of asthma, directly after a snake-bite, or, more familiarly, to prevent a fainting. In the same manner it lowers the temperature in fevers. It also possesses analgesic powers, and, in combination with carbonic acid, is exceedingly grateful to an irritated stomach, either in the form of champagne or brandy and soda-water. It certainly possesses very considerable diaphoretic properties, especially to those of a sanguineous nature, and I think there can be little doubt about its diuretic action, although Hale

White remarks that it acts as a *mild* diuretic, this probably being a secondary result of its vascular effects. On the other hand, Rabuteau states that alcohol is one of the most powerful diuretics, and I am inclined to agree with him, both from clinical and general observations.

It is interesting to note that in London, during the last few years, the number of diuretic conveniences has been enormously increased. It would be unreasonable to suppose that these would have been erected unless to fulfil a real want. This want is caused by the enormous quantity of whisky (direct alcohol) now consumed in comparison with beer (diluted, or indirect, alcohol), which used formerly to be the popular beverage. Alcohol is also a hæmostatic, acting by constricting the smaller vessels; it is also a food in a limited sense, but far more is it a conservator of force. Finally, its powerful antiseptic action must here be considered. No bacterium can exist in its presence, even in the state of spore; for generations specimens in museums have been preserved in it. Our *parts* in the dissecting-room were washed with it and wrapped up with cloths soaked in it to prevent them from corruption, although in the days I speak of we were unaware of the why and the wherefore of its action, for bacteriology was a science yet to come.

The study of the antiseptic properties of alcohol takes me back a good many years—as far back as the close of the great war between France and Germany, with the internecine strife that immediately followed it. I remember then being struck with the remarkable cleanliness exhibited by wounds after being washed and dressed with alcohol. This was at the Hôpital Beaujon in Paris, which lies close to the place through which the Versailles troops effected an entry into Paris; consequently we had many wounded in the final struggle, besides those accounted for by German bullets and shells. The only dressings used at that time by M. Dolbeau were alcohol and glycerine, another product of yeast fermen-

tation to be presently described. Sinuses formed in the track of bullets did wonderfully well when syringed out with alcohol, which seemed to find its way into interstices and clean them out in a way I have never seen with any other substance. I rather think that there used to be a certain amount of pain attending the alcohol dressing, but pain was not much considered in those days. Had we known the reason of our wounds being so beautifully clean and free from suppuration, we should have also known that they did not require dressing so often.

Glycerine.—This is another substance which we used very largely, soaking charpie in it, and laying it in the bottom of wounds. It is a triatomic alcohol, possessing great solvent and hygroscopic powers. It controls metabolism and retards fermentation, but aids digestion by dissolving the pepsine. It exercises a direct influence on nutrition, and, like alcohol, is a food of conservation.

Succinic Acid.—This is chiefly used up in the system and transformed into bicarbonates, which increase the alkalinity of the blood. The remainder appears in the urine in a state of combination, in which state it possesses antiseptic properties.

Dr. Caravias deemed it of such importance in the treatment and dietetics of the phthisical state that he recommended the systematic employment of succinogenic substances in such cases. He advises, therefore, raw meat, fats, bimalate of calcium, benzoic acid and its salts, non-acidulated pepsine, asparagine, carrots, green vegetables, etc.

From the physiological actions and therapeutics of the products resulting from the vital action of yeast cells, we pass on to consider the therapeutics of the protoplasm and constituents of the yeast cell.

We have already seen from the analysis on p. 19 that the protoplasm of yeast cells is distinguished by the large amount of phosphorus it contains, thereby resembling the leucocytes

and blood plasma in their chemical constituents. The nucleins also obtained from yeasts differ very little from those of animal cells, and both of them may be converted into spermine, the active principle of the emulsion designed by Brown-Séquard. This substance, spermine, has been especially studied by Professor A. Poehl, of the University of St. Petersburg, who obtained it from the testicles and prostate glands of young bulls and stallions. The result of his experiments proves that this substance is an intra-organic ferment or enzyme of oxidation, which acts by destroying the metabolic basic products of waste or denutrition (leucomaines), which are thus oxidized and eliminated from the system, thereby preventing that auto-intoxication to which so much attention has been recently directed, and which is, no doubt, a state of system which predisposes to invasion by the pathogenic microbes.

Poehl is of decided opinion that a state of resistant immunity is maintained by the constant action of spermine upon the leucomaines, which gives to the animal most of its heat and energy. When from any cause (such as bacterial infection) the leucocytes do not secrete a sufficient quantity of spermine, the blood becomes less alkaline, so pernicious results ensue. On this subject the reader is referred to the excellent article, by William Armstrong, on 'Gastro-Intestinal Toxins' (*B. M. J.*, July 31, 1897), and Poehl's communications (*Therap. Monat.*, January, 1891, and *Wien. Med. Woch.*, 1897, No. 4). Many observers consider that the serum of the blood owes its bactericidal power to this substance. In the hands of Veliammoff and Roshtchinin it has done good work, both in sustaining exhausted patients through prolonged operations, and in cases of diabetes mellitus, tuberculosis of lung, and in neurasthenia. The latter author considers that, on account of its power of strengthening the energy and vital capacity of the cerebro-spinal nerve elements, of generally increasing the vital energy of

the system, and of regulating cardiac action, 'a brilliant future can be safely expected' for it (*Vratch*, No. 10, 1891, p. 282).

Nuclein is secreted especially by the large polynucleated (neutrophile) cells. Now, these are the very cells which possess the greatest phagocytic power. Let us imagine, then, the system of an individual to be in a state of slight auto-intoxication, that is, with an under-average amount of nuclein circulating in the blood, becoming invaded by bacteria; the neutrophile cells hurry to meet the invaders, upon which they exercise their phagocytic power. Yet they have been caught whilst unprepared, and it is too much for them to do to secrete the nuclein needed for the system, and exercise phagocytosis at the same time; consequently, they lose the battle, and the system becomes definitely invaded. The old-fashioned practice of cleaning out the primæ viæ by a brisk purge at the first symptoms of an attack was sound practice, to which we are reverting, for by so doing toxic matters were at once got rid of, and the liver encouraged to secrete more bile, that most valuable of all neutralizers of poisons produced during digestion, to toxiptones, ptomaines, etc. Most efficacious, too, is another old-time practice, that of administering an emetic at the initial symptoms of infectious disease. I have personally seen the good effects of this scores of times; in fact, one of the most eminent physicians of the present day—and certainly the most eminent as regards treatment—told me in conversation, a quarter of a century ago, that it was a standing order in his house that if he were absent, and one of the children should sicken with feverish symptoms, with headache and sore throat, with or without rash, a certain emetic was to be given pending his advent. Should he do me the honour of reading these pages, no doubt he will remember the time when his children were little, and how great was his solicitude for them. These measures not only clear out many bacteria, but free the digestive organs, and set free a certain portion of nuclein to deal with the bacterial products.

Nuclein obtained from yeasts, eggs, spleen, thyroid gland, pituitary body, etc., as well as from the testes, has been largely used by Dr. Vaughan in America, both by means of subcutaneous and intramuscular injections and by oral administration. It has been used by various investigators for various diseases—diphtheria, follicular tonsillitis, pseudo-diphtheria, and pulmonary phthisis—in all of which a distinct improvement or arrest of the disease was noticed. The nuclein appeared to have a dynamogenetic power of increasing the nerve tone of the system, in addition to its being an auxiliary to the protoplasm of the leucocytes in rendering inoperative the attempt of the invading bacteria to effect a foothold, multiply with fermentation, and so produce disease. If such good results can be obtained with nuclein alone, how much better must be the effect when they are carried to the hard-pressed leucocytes, not in an abstract condition, but in the living, healthy state by auxiliary cells, which also possess phagocytic properties. I have lately made the addition of a certain amount of artificial nuclein to the yeasts prepared for injection to be used in cases of phthisis, and I have been very pleased with the results obtained so far, but the regulation of the dose requires great care.

There remains but to discuss the therapeutics of the mineral substances contained in the protoplasm of the yeast cells, and see how far their peculiar components are of service or antagonistic to the human economy. These mineral matters are very important items in the animal system, for upon them many important processes depend, the action of ordinary table salt upon vegetable-eaters being an instance. Minerals are indispensable to the economy, for Forster has demonstrated that an animal deprived of all mineral matters dies much more speedily than when deprived entirely of food ; this can be explained when we consider that during the assimilation of albumin a good deal of sulphuric acid is set free, which in the normal state is at once combined with the mineral bases

in the food ; but if these are cut off, the free acid either combines with certain salts taken from the tissues, which really require them for other purposes, or it exercises the corrosive action of its free state upon the general economy. Normally we find these minerals in the system combined with organic acids, in which state they play a very important part by exchanging these organic acids for the mineral acids formed during assimilation for one thing, and for another by preserving the economy from an accumulation of products which would be detrimental to the chemical and physical processes of the tissues ; they also form the alkaline carbonates as a final product of combustion. Many of them possess special properties over certain organs and cells, where they may be found in combinations with protoplasm, giving rise to special reactions. A glance at the analysis of yeasts will show that their mineral constituents are the very ones that go to build up the organs of higher functions, being especially rich in phosphates.

The modes of administration fall into three principal divisions : (α) By direct application to the part affected ; (β) by direct administration to the mucous passages ; (γ) by direct administration into the fluids of the system.

(α) On foul wounds and ulcers on the surface of the body, pure yeasts may be applied, either by means of the cartouche and syringe, in the form of backérine, or, what is still better, in the form of a dry powder. This must be very lightly dusted over a wound which has been previously cleaned by a stream of sterilized water ; as a general rule, one application in the twenty-four hours is enough. It is astonishing to see how quickly large varicose and other ulcers heal up under this treatment ; cancerous wounds also often do exceedingly well. The powder must be kept dry, but not in too warm a place ; if these conditions are observed, it will retain its properties for some time. The powder is very difficult to make, but the laboratory difficulties have been finally overcome by

M. Lachenaud, and we now get a powder containing two-fifths of pure yeasts. This powder is excellent for blowing on to the diphtheritic patches on the throats of children, who are too nervous and terrified to permit the application of the spray, and as it adheres to the membrane, whilst destroying the bacilli causing it, the powder does not require to be used very often.

A very beneficial effect is found in the direct application of yeast spread over warm linseed poultices; the poultices must not be *hot*, or the yeasts are destroyed. This means is especially useful in cases of ischio-rectal abscesses after they have been opened or have burst naturally.

(β) Yeast may be administered by injection into the rectum, which is found useful in cancer of that organ, or by injection into the mouth, throat, or through the nostrils, which is of great service in cases of diphtheria in which the nasal passages are implicated. By intratracheal injection, which is effected by first putting the glottis under the influence of cocain, then passing an appropriately curved silver tube through the vocal cords, when the backérine can be syringed through the tube into the lung; this is chiefly of service when microbic associations are present in the lungs of phthisical patients. It is of distinct service, but needs a steady hand and good eye, with no little co-operation on the part of the patient. The lungs can also be reached by means of a spray or nebulization, which may be preferred to the fluid injection. The same means can also be used up the nostrils, to the pharynx or throat generally. An ordinary Clarke's spray answers very well. Oppenheimer's nebulizer may be used for inhalation, but it is an uncertain instrument, and wants perfecting for this substance; I have, however, seen good from its use. The way I most recommend is to attach the bellows to an oxygen bag, and send oxygen instead of air through the yeasts, which are then inhaled into the lungs in a very active state; the oxygen should first be

warmed through an oxygen warmer, as designed by Henry Robson, of Leeds. I have lately seen a most excellent powder nebulizer, made by Ferris, of Bristol, by which the dry powder (p. 127) could be conveyed to the lungs with advantage; it can be used with the oxygen tube.

Yeast may be ingested or swallowed either mingled with beer, honey-and-water, or made into a paste with honey, or even plain brewer's yeast may be taken as it comes from the brewery. It creates at times somewhat annoying symptoms when taken in this way, causing a feeling of distension, with eructations. This is the way in which it has been given in furunculosis and diabetes, usually in tablespoonful doses.

Yeast is a very old remedy for the former complaint, and has been revived for the latter recently by Cassaet (*Lancet*, 1895, ii., p. 685), who recommends a dose of 2 ounces; this amount may produce diarrhœa occasionally, but not so frequently in the diabetic, who are usually very constipated.

(γ) Hypodermic injection is the mode recommended for the general treatment of the various diseases, with the other modes in addition where opportunity offers. In our own hands, and in the hands of those who have been educated in the use of the special syringe, we have never had any mishap; patients almost invariably feel the actual flow of the backérine under the skin far more than they do the insertion of the needle through the skin. This subcutaneous method is the one we generally practise; parenchymatous, intramuscular, and intravenous injections have been used, but none of them possesses any advantage over the more simple subcutaneous injection, with which everybody is familiar.

The choice of spot to be selected for the injection depends upon the distribution of the yeasts within the system, as well as the particular malady to be treated. In phthisis a very good spot is over the supraspinous region of the scapula on the affected side, or, if both sides are affected, then on alternate sides; if the spot of insertion should remain pain

ful, the next injection may be given in the arm near the middle of the deltoid muscle, or (which I personally prefer) a spot just above the level of the angle of the scapula, and in front of its anterior border.

In general tuberculosis, the abdominal tuberculosis of children, and in typhoid fever, the left flank, just below the spleen, is the best place ; and if there is the least distension of the abdomen, the left side should be chosen. I have not found that extreme sensitiveness in that region amongst English people that De Backer has spoken to me about and mentions in his work (p. 285), except in those cases of phthisis who were compelled to breathe entirely by abdominal respiration, thereby inducing constant movement and friction of bedclothes over the spot of puncture.

In cancers, the choice of spot depends very much upon where the growth is situated. There is no great objection to injecting directly into the neoplasm, but, bearing in mind Snow's assertion that any puncture in a growth may temporarily reduce its bulk without in the least arresting, or even retarding, its progress, I am of opinion that it is better to inject into the most contiguous tissues, rather than into the growth itself, or the injection may be divided, and part given each way. There is also another reason for not injecting into the growth itself, for by so doing we are injecting into degenerating cells and tissue, whereas if we inject into the periphery or neighbourhood, we are injecting into the line of the radiation of infection, by which the youngest cells are met with and destroyed.

In cases of mammary cancer, a spot may be taken at the lower origin of the pectoralis major, as the yeast cells get taken along in the same stream and direction as the cancer cells must travel if set free. In cases of cancer of the stomach, the epigastrium or splenic region offers the most advantages ; in cancer of the uterus, the thigh or buttocks may be chosen; where the kidneys are the victims of cancerous

growth, the region of the back about the insertion of the quadratus lumborum is a favourable place; in cancer of the tongue, lips, ears, and glands of the neck, the choice of spot is much more difficult; perhaps the best place is either in the subclavian or inferior carotid triangle of the neck. De Backer has just (September, 1897) written to me concerning a most successful case of epithelioma of the lip cured by minute injections (a few drops) administered into the chin. In this case the patient is bearded, and the injection was given through the hair.

The reactions that happen after injection deserve mention, so that patients may be warned as to what they may expect. The reaction occurring in a healthy individual has already been described; we are here dealing with what happens to patients. Reactions of some kind or another almost invariably take place, so that we are often able to cast a prognosis from observing them. In rare cases no reaction occurs; De Backer mentions the case of a patient suffering from laryngeal phthisis who had received four injections, given at five days' interval between each, but who showed no reaction of any kind from first to last; in this case there was no improvement. In one of my own cases, a gentleman seventy years of age, suffering from cancer of the submaxillary glands secondarily to an amputated lingual cancer, no reaction whatever was observed, much to the surprise of both of us, for De Backer had come over to London to see him with me. We made a special culture of backérine for our patient, and thinking that perhaps the injections in the close neighbourhood of the growth might not have been absorbed, we administered the next in the flank, yet with no result; the other flank was tried, and one day we even gave him two injections, but always with the same want of success. The patient died a few weeks later, but suffered very little or no real pain since the time the injections were first administered, beyond the mechanical difficulty in swallowing. This patient was also

the subject of Raynaud's disease, which might have had something to do with the peculiarity of want of reaction, and might betoken an extreme lack of vitality.

On the other hand, the following is a case of no reaction following injection, but the treatment resulted in a cure. A lady of about twenty-six years had had repeated attacks of influenza, which left her intensely neurasthenic; for years she had suffered from an occasional discharge from her ears, the result of an attack of scarlet fever in childhood. Her mother had died of phthisis, but the rest of the family were healthy; her organs appeared to be sound, but the urine was peculiar, occasionally being extremely offensive, and was found to be swarming with bacteria. Koch's bacillus I could never find, though I more than suspected its presence. She was very pallid, and incapable of any exertion, insomnia being also a distressing symptom. This lady, after consulting numerous physicians and undergoing various treatment, Weir Mitchell's included, without any improvement, came to me for treatment by pure ferments, as I was under the belief that she was suffering from the effects of bacterial toxins. Accordingly she was injected in the left side over the abdomen, about 6 p.m., at the beginning of May. During the night the temperature only rose 1 degree, and beyond being thirsty during the night and sleepy in the morning there were no unusual symptoms; the heaviness persisted slightly till evening. The following night was good, and the next day she went out driving. Between May 10 and the middle of July she received four injections with never more reaction than the first—so little, indeed, that she has been out on her bicycle the very next morning without discomfort. Although without much reaction, the treatment has not been without result, for the patient quite recovered her health, and was a different being before the end of the summer. Her recovery may have been due to her leucocytes having been aided in their nuclein-secreting properties, and from that timely aid

are now in a flourishing condition, as she has not required medical attention since.

The description given in the previous chapter of a reaction happening to the healthy human subject may be taken as a type of what generally occurs to those under treatment, with certain exceptions. I find generally that those suffering from disease experience a much greater elevation of temperature (in some cases even rising to 104° Fahr. at the crisis), hence the mental excitement is usually greater as the period of rigor approaches, very much resembling the hilarity caused by drinking champagne. One lady has particularly noticed this, and has spoken to me of her husband's backcrine voice.

Patients may have hallucinations, and imagine that they see people standing about their bed, talking at them, mocking them, or making faces at them, though this is not often the case. One of my patients, however, a short, thick-set, very powerful man, yet with a sensitive nervous system, during the night after an injection, got out of bed, staggered about the room and threw things about, but he is a very excitable man naturally. All patients, with very few exceptions, talk a great deal, and perhaps may say more than in their more cautious moments they would deem prudent—another likeness to the effects of champagne.

As the excitement is greater, so is the after-depression more intense. Many of my patients tell me that they wind up with a good crying fit, after which they are better; others, that the depression takes the form of crossness, fretfulness, or downright ill-temper. There is one very frequent symptom complained of by phthisical patients, which is a peculiar taste or odour in the mouth, and some have said in the perspiration. This may be due to the excretion of bacillary products. It is difficult to describe a sensation that one has not experienced one's self. One patient described it to me as a taste of herbs or decaying leaves; another, as a sort of chemical taste (whatever that may be); another, as an indescribable

taste; and yet another, as 'a dreadful taste which I cannot describe.'

As regards the urine, there may be either a partial suppression, or just the reverse—a very free micturition. The bowels are more likely to be constipated than free in their action; indeed, one case of early phthisis with diarrhœa was much benefited by this treatment.

Many of my patients also mention pins and needles, or little cramps in the limbs; these come on after the shivering and before the sweating stage—*i.e.*, in the period of dry heat. The following account taken from my case-book gives a very clear idea of what one may generally expect.

Saturday, 9.30 *p.m.*—Injection of half-tube of backérine into the subcutaneous tissue lying over the supraspinous fossa of the scapula. The patient went to bed at 10.30 p.m., but could not sleep at first, being somewhat excited at the novelty of the injection, and the hope of a cure (this was afterwards happily realized). At 12.15 a.m. (Sunday) the limbs began to feel like pins and needles, the point of injection being rather painful; the whole shoulder and arm, from neck to elbow, aching and feeling stiff, and the arm could only be moved with difficulty.

In about a quarter of an hour shivering commenced all over the body. till the bed shook and the teeth chattered. This lasted about twenty minutes. Shortly after the rigor had ceased, the skin all over the body seemed painful and cold to the touch, though the patient inwardly felt warm. This was said to be an indescribable feeling, which lasted from a quarter of an hour to twenty minutes, when a feeling of great heat came on, with profuse perspiration and headache, the head feeling like two. The shoulder became more and more heavy until, in the morning, the arm could not be raised; an odour was appreciated in the perspiration, and an unpleasant chemical taste in the mouth. The patient then went off to sleep and slept till seven, waking with a feeling of depression,

and with aching limbs. There was very little appetite for either breakfast or mid-day dinner. She had no inclination to get up, so stayed in bed dozing till six in the evening. The spot of insertion was slightly swollen in the morning, becoming less so in the evening, though it then appeared rather red. She got up at six o'clock, and came to my house at seven. I found the shoulder stiff and heavy, but the headache and depression were quite gone. She looked a little pulled down, as if after a dissipated night. No urine had been passed during the night, but a large quantity had been passed since eleven in the morning, and before coming to me. The next day (Monday), after a good night, the patient was quite well again, only the shoulder still remained a little stiff. This was a reaction after a first injection ; succeeding ones are generally of a milder character.

The amount of dose is the next point which claims our attention. Like all medicines, backérine has to be regulated according to the age of the patient, and a little according to weight. The cartouche tubes are constructed to contain 1½ c.c., but they are seldom quite full, neither do we ever inject the whole of the contents, so that we may say that the standard dose is 1 c.c., which is estimated to contain on an average about 2,000,000 saccharomyces cells. For an adult, it is our usual practice to commence with half a tube, and if this produces a marked reaction, we continue with the same dose ; but if less marked, we increase the dose to three-quarters of a tube for the second injection, to the full dose for the third. There is never any need to administer a larger dose than the contents of a cartouche, always stopping short of a point just above the place where it becomes contracted. In the experiment made upon the person of M. Bruhat it will be remembered that 6 c.c. were administered, and that a good deal of glandular discomfort was the result. The following case is illustrative of the effect of a big dose : I administered a full dose (rather more than 1 c.c.) to a dog weighing about

10 pounds. It was the second injection; the first, given a week previously, had not been very successful, owing to the struggles of the animal. The dog was old (thirteen years), and showed signs of age; she was suffering from cancer of the mammæ. There was one large growth, the size of a good big walnut, in the lowest mamma of the right side, a lesser one in the next on the same size, and two of the same size in the corresponding mammæ of the left side. The injection was administered into the subcutaneous tissue of the abdomen in the central line; it had a very powerful effect, and for two or three days she was very ill, the diseased parts being much swollen, and painful to the touch. The hind-legs seemed partially paralyzed—anyhow, she made no use of them in progression; there was also much thirst, but she appeared to have a difficulty in moving her mouth and tongue. At the end of the fourth day she was much better and more lively, but did not move about much, as the hind-quarters were still weak, the legs being inclined to give way and double up; the swelling and tenderness had disappeared, and all four growths were much shrunken. This dog had other injections afterwards, with arrest and shrinking of the larger growth; the smaller ones became hardly perceptible, and from being an emaciated bag of bones, as she was before the treatment commenced, she became quite fat, and as frisky as became her years. That is eight months ago, and I hear that she keeps well, though age is telling much upon her. Now, this dose in a dog of that weight would correspond to one of nearly a fluid ounce in a man of my own weight; but such doses are not necessary, and from the doses that we advise we have *never* seen any harm result when properly administered. For children the following standards are recommended, it being understood that the first injection should be but half these quantities:

15 years old	...	...	...	...	$\frac{3}{4}$	of a tube.
10 „ „	...	...	...	...	$\frac{1}{2}$	„ „
5 „ „	...	...	...	...	$\frac{1}{4}$	„ „
3 „ „	...	...	...	...	$\frac{1}{10}$	„ „

I have administered this latter amount to a child aged fourteen months, suffering from tubercular meningitis; but although there was reaction, yet the remedy came too late, and death ensued. The observations made on this case lead me to think that if the treatment could be commenced when the earlier symptoms only are present, such as change of the child's character, purposeless vomiting, with constipation, hydrocephalic cry, dislike to light and noise, etc., the whole disease might be arrested.

The frequency of the injections is a difficult point upon which to lay down rules, as the diseases differ as well as the individuals suffering from them, hence every case must be judged on its own merits. Experience alone can guide us definitely, though the following suggestions will be found to be of service. From the time of the first injection of half a tube to the second, a week should elapse, the same interval being observed between the second and third. Should the place of insertion remain painful or swollen, the interval may be widened out to ten days. After the third injection, four or five more may be given, with a week or ten days' interval between them; then, as the system begins to get the upper hand of the disease and shake it off, the interval can be gradually lengthened to once a fortnight, once in three weeks, once a month, and so on until health is completely restored. Should any intercurrent acute attack supervene, the intervals should be again contracted.

A few clinical hints and instructions will be found of use. The needle is best sterilized by leaving it, after removal of the wire, for a few minutes in pure alcohol; eau de Cologne answers the purpose admirably, and if this process is repeated before putting the needle back in the case, the inside channel will never rust. Before the end of the cartouche is filed off, it is a good plan to push the cartouche well home with the fingers and thumb of the left hand through the fenestrations of the syringe; by so doing no broken glass can possibly be dis-

engaged after the screwing on of the needle, when the piston is made to act. The filing should be effected as closely as possible to the syringe; a few light strokes are all that is necessary, for if the file just bites the glass it can be snapped off quite cleanly, but if the filing has been too vigorous the narrow end of the cartouche will fly off. This does not matter in the least, but may be disconcerting to a novice with the syringe. In either case there is always a kind of *spit* more or less marked; this is owing to the removal of the pressure and commencement of fermentation. The needle should be now taken immediately from the alcohol, waved or shaken in the air to get rid of the alcohol, and screwed on with as little delay as possible. The next point to observe is that all works well and smoothly. I always hold the syringe with the two first fingers of the right hand round the crooks, and the head of the piston-rod resting on the ball of the thumb near the insertion of the adductors, the needle pointing perpendicularly up in the air. By holding the syringe in this way a powerful steady pressure can be brought to bear in a direct line upon the plug of the cartouche, and a little of the fluid is allowed to trickle down the needle; this has the additional advantage of washing away any alcohol that may remain, besides that of expelling any air from the apparatus, which is one of the objects aimed at in holding the needle upwards. The other object is that we can see much better what we are about and obviate a loss of fluid; for those unaccustomed to handle the syringe may be surprised at first to find the amount of force necessary to move the plug; sometimes it moves rather suddenly and with a *squish*, which means the loss of most of the contents of the tube if the syringe is held downwards. With improved plugs, and by using only the best English glass of the same calibre throughout, this does not now often occur, but the plan should be adopted nevertheless. The use of the syringe is soon acquired.

I find that the mode of insertion least painful to the

patient is to hold up a fold of skin, and, whilst retaining it rather tightly between the finger and thumb of the left hand, to thrust the needle deeply, at right angles to the pinched-up portion, into the subcutaneous tissue. The fluid must not be injected too rapidly, as it causes some distension, but directly the quantity intended has been administered, the needle must be very quickly withdrawn in order to prevent any fluid following on in its track. A little gentle massage aids the dispersion of the backérine. Some patients will tell you that they feel the sensation of the fluid at once running down to their elbow or wrist, with a feeling of heaviness in the limb. The needle must now be returned to the alcohol (a minim measure is a capital receptacle), whilst the cartouche is removed from the syringe and thrown away ; we never use this a second time, not even the plug ; finally, the needle is threaded with its wire and everything returned to its case.

Although it may seem to some, perhaps, that I have entered into needless detail of obvious matter, to many who have to deal with a new instrument and new idea these little details are of importance in making them feel at home with them, and not likely to be put out by any little contretemps that may arise. I have seen blunders of injection committed from too great timidity, the skin being transfixed at a too acute angle, the subcutaneous tissue being scarcely reached ; this gives great pain to the patient from the stretching of the layers of the true skin. I have also seen a blunder from too great boldness, the depth of the puncture only being terminated by the point of the needle impinging on a bone to the detriment of the former. Blunders also connected with the cartouche, one of which occurred in De Backer's practice, will be related presently. There is one hint connected with the cartouche that should be remembered, which is to see that the little piece of drainage-tube is always on the narrow end, otherwise it will smash in the syringe directly the pressure of the piston is exerted.

There are yet a few points to mention. We sometimes see at the point of injection a red tumefaction, painful and hot—that is, with all four classical symptoms of inflammation. We may think even that there is fluctuation, but let us not persuade ourselves that it is an abscess which has formed, and so put a knife into it, for the probability is that it is nothing more than a local leucocytosis, gentle rubbing with warm camphorated oil being all that is needed. In subsequent injections to the first, physicians will meet with the curious fact that sometimes the spots of previous inoculations will become tender again; so also will spots into which other injections (morphia, strychnia, mercury, etc.,) have been made. Of course, abscesses may occur when aseptic precautions are not observed. The following is the case of an abscess arising from excessive care, without due grasp of the principles of the treatment. De Backer relates the story that a physician becoming acquainted with backérine for the first time, and being habituated to the clear fluid of antitoxins, was under the impression that the sediment in the cartouche should be dissolved, and, as shaking did not render the fluid limpid, he conceived the idea of dissolving this seeming precipitate by heating the tube in a water-bath. This of course killed the cells then and there, but the liquid did not become clear, yet, having done his best conscientiously, he injected this quantity of dead cells, which really did produce an abscess. If an abscess should form in consequence of the injection of the contents of any of the tubes sent out from the laboratory, it will probably be due to want of proper care and aseptic precautions on the part of the operator, and in spite of the saccharomyces cells. It is a good plan to cleanse the skin in many patients over the region of intended puncture either with eau de Cologne or æther, which is also said to mitigate or abolish any pain that might arise in the inoculation.

Patients often want to know when they may expect reaction. Rigors or simple chilliness may occur any time from

two to five hours after an injection, the interval decreasing generally after the first injection. Some patients experience a peculiar secondary reaction from three to ten days after an inoculation. Perhaps the first thing we can notice is an increase in the tension of the pulse, which will even show itself before the backérine voice and exalted talk commences. This high tension is a point that often demands a considerable amount of skill and judgment in the administration of backérine to patients of advanced ages, in whom the arteries are hard and tortuous. I am inclined to think that the paralysis of the hind-limbs, etc., of the dog mentioned on p. 135 might have been due to the effect of the backérine upon the vessels of the brain ; nevertheless I have administered it in a case of a patient who had had already two attacks of hemiplegia without any bad effects whatever ; on the contrary, a cure of the disease (diabetes).

The after-treatment of an inoculation should be conducted on general principles, the rigor treated by hot bottles and extra clothes, the perspirations by sponging and then drying the body by light hand-rubbing over a warm towel. Any demulcent drink may be given during the consequent thirst, and for the depression and bad taste in the mouth a little weak brandy and soda-water is very grateful to the patient. It is well that cold should be carefully guarded against for a day or two after the injection.

From considerations of the physiological action of the products and constituents of yeast cells, which explain the phenomena that accompany their introduction into the human body, with due consideration also to the best means of introducing them and of dealing with the phenomena produced, we now proceed to the exposition of those diseases in which we might reasonably expect the treatment by pure ferments to be of service. The results we have obtained will be described, as far as space will allow, under their various headings, but many will have to remain for future works dealing with each disease eparately.

These diseases fall into two divisions : those due to bacterial pathogenic fermentations and those due to disturbance of the glycogenic functions, though I do not mean by this to deny that these may not also be due to bacteria ; indeed, I think we shall eventually find that it is so.

Division I., Class A.

Diseases due to recognised bacteria :

1. Tuberculosis.
2. Diphtheria.
3. Ulcerative Endocarditis.
4. Typhoid Fever.
5. Puerperal Fever.
6. Septicæmia.
7. Pneumonia.
8. Malaria.

The latter not being due, however, to bacteria strictly speaking, but to exceedingly minute endozoa. To the above list we shall have to add yellow fever (Sanarelli) and rheumatic fever (Achalme), owing to recent discoveries, and before long no doubt cerebro-spinal meningitis and others will have to be added to the list.

Class B.

The ferment has not been isolated, or has not yet been universally recognised.

1. The Exanthemata.
2. Whooping-cough.
3. Syphilis.

Some readers will doubtless be inclined to quarrel with me for putting syphilis in this class, being believers in the vibrio or bacillus of Lustgarten ; but as this bacillus has never yet been cultivated or grown in any media outside the body, eminent authorities state that its existence is problematical. Experts further tell me that they can produce such appearances as the vibrio described, by manipulation with the dyes in healthy tissues.

Division II.

Diseases due to disturbance of the glycogenic functions :

1. Furunculosis.
2. Diabetes.
3. Cancer.

CHAPTER VIII.

DIVISION I., CLASS A.—TUBERCULOSIS.

This disease, though essentially bacillary in its cause, the particular bacillus being well known, differs so much from all others of the same class and division that it deserves a special chapter to itself. Truly indeed does Professor Charles Richet say, in his address to the British Medical Association at Montreal, that works on tuberculosis written fifteen or twenty years ago belong to another age, appertaining no longer to medicine, but only to its history. I have before me a standard work on medicine, with the published date of 1886, in which the following statement is made: 'We must conclude that the infectious virus which excites the tuberculosis is not introduced from without, but is generated by the animal itself, and that, given the diathesis, any kind of inflammation, set up in any way, may call forth tuberculosis.' Only eleven years have passed, and yet it seems to us now utterly incredible that such statements could ever have been made, yet it represents very fairly the opinions then held. This article indeed belongs to another age, although the author appears to have a slight glimpse into the future, as he remarks farther on: 'Some have suspected that infective particles may be inhaled by the lungs.' Finally, the author mentions casually in the concluding paragraph that 'more recently Koch has announced the discovery by him of a specific tubercular organism in tuberculous structures, and

in the sputa of phthisis.' Yes, indeed, it is to the laborious researches by Robert Koch that we owe the discovery of what these 'infective particles' really are, what is their life-history, and how the terrible effects of their sojourn within the human body are produced.

In this chapter all subjects of controversy will be avoided as much as possible; only what is known and what is generally now accepted will be stated, with that which particularly bears upon the object of this volume.

Tuberculosis, whether general and acute or local and chronic, is a true zymotic disease produced by the rapid or slow fermentation (as the case may be) of a formed ferment, which is the particular bacillus discovered and differentiated by Robert Koch in 1882, and is generally known by the name of the discoverer, who did not, however, publish a full account of it until the year 1884; it is a true bacillus, but is very minute, varying, when examined in fresh sputum, from 2·5 to 4 μ long, with a general thickness of about ·2 or ·3 μ, being therefore very short and slender; it is non-motile and grows best at the normal temperature of the body. For a long time it was found to be difficult of culture, but at the temperature named it will grow very well, though slowly, on blood serum, more rapidly on glycerine agar, also on potato and other vegetables, the great point being not to have the layer of medium too thick. The author has found a thin slice of potato dipped in hot bouillon and allowed to get cold to be a very good medium of culture. This bacillus is by no means easy to stain by ordinary methods, but it can be very well accomplished by using the Ziehl-Nielsen double stain or its modification by Fraenkel, which is much more expeditious and gives beautiful results; it is the one invariably used now in the author's laboratory.

Koch's bacillus possesses very great powers of resistance, especially when dry, and it is owing to this resistance that its ravages are so great, yet a temperature of 70° C. is always

fatal to these bacilli if young, but when old and sporulated they require either a long exposure to this heat or a greater temperature still before they are rendered inert. In so small and slender a bacillus, sporulation is not always easy to detect, yet with careful staining we can see the protoplasm cockle itself up into several particles within its containing envelope, these particles being much more highly stained than the rest, and it is certain that when the bacilli are in this state they are much more resistant to adverse influences than when the protoplasm appears to be homogeneous. When moist, these bacilli cannot resist the action of direct sunlight; even the ordinary diffused daylight of the laboratory will kill them in a few days; the less the sunlight, the longer their endurance, especially when sporulated; the drier they are the more resistant they are also; hence we can easily conceive the mischief that must ensue from the filthy habit of constant expectoration so freely indulged in by the lower orders, in houses and in public places also, a notable example of which is an ordinary third-class smoking compartment, where the dried sputa are kicked into the air by the feet of many. This, indeed, is a potent factor in the cause of the spread of phthisis in large towns, more especially in winter, when the hours of possible sunlight are very few, the very sunlight that we do get being robbed of most of its actinic rays in its passage through horizontal layers of fog and heavily laden atmosphere.

Dried sputum will retain its virulence unimpaired for months, which can be easily understood when it is considered that many of the tubercle bacilli are enclosed in a tenacious lump, so that those in the interior never get exposed to malign influences until those outside have perished and fallen away, together with the substance that held them together. They probably do not increase and multiply outside the animal body, because the conditions favourable or necessary to their growth are somewhat

numerous, and not likely to be found all together at one time nor in one place.

Carbolic acid, mercuric perchloride, and formalin very quickly destroy them, but gastric juice does not kill them nor does a temperature of – 3° C., though they do not grow in that temperature, but merely exist resistantly.

The means by which the tubercle bacillus can invade the human system are :

1. Direct inoculation.
2. Inhalation.
3. Ingestion.
4. By the genito-urinary tract.

1. The First Method — that by Direct Inoculation—is certainly one of the rarest forms of invasion in mankind, although it is the form chiefly made use of in experimental tuberculosis ; yet it can and does occur : an instance in point is quoted in Green's 'Pathology' (p. 397), and that it can also occur from post-mortem wounds I know full well, from an accident that happened to one of my friends who received a scratch whilst conducting a post-mortem upon a guinea-pig that had been artificially rendered tuberculous. Fortunately, being of splendid physique and constitution, the evil effects upon him were entirely local. A further case may be cited which was brought before the Harveian Society on October 21, 1897, by Mr. Bulleid. This was a tumour in the axilla, which on removal turned out to be tuberculous, originating from a wound in the elbow some six years previously. For another reported case, the reader is referred to one by Professor Oscar Liebreich, *Lancet*, October 2, 1897.

It is quite impossible for the bacillus, non-motile as it is, to penetrate the sound skin, nor even the uninjured and intact mucous membrane ; and there can be little doubt that children, who are always rolling and tumbling about, and who are never so happy as when playing with dirt, frequently get

portions of their skin abraded, and upon these abrasions the tubercle bacillus falls or may get rubbed in, this very bacillus perhaps having been shortly before expectorated from some person's lung, to find here a lodgment and new home. How often do we not see the neck in children and young women to be the seat of glandular enlargements. Now, the skin of the neck is exceedingly thin, and yet custom has it that in these two classes of people the neck should be one of the most exposed regions of the body. Enlarged, that is, infected, glands are far more often seen in those children whose surroundings are limited in their extent only, but not limited in their dirt and insanitary conditions generally. These are not the children who are hurried off to have their faces and hands washed as soon as they come home; the poor have little chance of cleanliness, for fuel is expensive, too expensive, indeed, to be used for the purpose of heating water merely for washing, a process which they have never been taught to consider a necessity to health, hence the cold water on a cold day is rigorously shunned.

I do not wish for a moment to throw any blame on the poor, for no one enjoys the luxury of a bathe in the Serpentine more than do the Arabs of the streets; but I blame those who impair their budding intellects by cramming them with too much predigested mental pap, whilst neglecting the hygiene of the body and leaving the unfortunate children to find out for themselves the grand laws of Nature as best they can—and what this *best* is the history of tubercle can show.

The infected glands are the police cells of the body. One will often hold the malefactor in its cells for years, when, perhaps from some defect of nutrition, the gland loses its power and the bacillus, finding its opportunity, escapes from its prison and revenges itself by more or less speedily contaminating the whole body. Can we not all recall some cases of consumption in which the history is of enlarged glands in childhood? The gland, when no longer able to hold its prisoner in check,

tries to get rid of him by external suppuration, and this plan of Nature to disembarrass the system of a dangerous inmate has been recognised and improved upon by the enterprising surgeons of the Royal Sea-Bathing Infirmary at Margate, who practise and recommend the early removal of invaded glands.

We have mentioned the resistance possessed by this particular bacillus, and its slow growth on media; so also in diseases produced by its presence we find the same slow growth (except rarely), a fixed determination to succeed, biding its time when vigorously attacked, renewing its activity the moment the chance arrives, all with inexorable patience. It may be asked, after what has been stated in former chapters concerning the natural defenders of the body, Why are the bacilli not destroyed by the lymph corpuscles in the glands? The answer is that, according to Metschnikoff, the new small lymphocytes possess no phagocytic powers, and that they do not acquire this power until some time after they have passed out of the gland and have become fully grown. In their infancy or early stage they probably have no power of secreting alexins either, and so their action against the bacillus or its toxins is nil. As regards the larger cells that come to the glands and those that were already there at the time of invasion, the probability is that the latter are actively engaged in breeding, and that the former come to the gland for that purpose, so that the most they can do, if they cannot kill their enemy, is to keep him safely locked up, and so prevent any entry into the efferent vessel of the gland. How they do this will be explained later on. By abrasion we may get that form of tuberculosis of the skin known as lupus vulgaris, which also affects the more exposed parts, such as the face. Without going into any controversy upon the subject, we may safely say that the balance of evidence is in favour of the tubercular nature of the disease. We never get lupus without being able to find Koch's bacillus somewhere in the diseased tissues, though I grant that it is often exceedingly difficult to

detect. It therefore behoves us to look a little closely into the conditions in which Koch's bacillus exists in lupus, when we shall see that although it is living in an aerobic state, yet it is subjected to a temperature considerably less than that of its predilection; hence the failure to produce lupus by direct inoculation with cultures or tuberculous tissues may be very probably due to these conditions not having been sufficiently recognised. In order to gain a possible result, it would be first necessary to cultivate the tubercle bacillus under the same conditions as obtain in lupus, and even in a temperature rather lower than that of the face if possible. These conditions being fulfilled, all that remains is to inoculate the skin of the face of a human being. In England such an experiment would be hardly possible, but the suggestion is offered to the followers of Kaposi, who deny that lupus is a form of tuberculosis.

2. The Second Method : the Invasion by Inhalation.—That the bacillus of tubercle is admitted into the body by means of inhalation has been abundantly and completely proved by experiments upon animals. It is the mode by which the majority of mankind are infected in early adult life.

What has been just now said of the skin applies equally well to the mucous membrane, that when sound it is perfectly impossible for it to be perforated by the non-motile tubercle bacillus. Unfortunately, however, in these days of manufacture, the air is loaded with sharp dust of all kinds, which irritates the mucous membrane, abrades it, and leaves it exposed to the attacks of the bacillus, which, when this is in a state of virulence, attains the abraded spot. This should seldom be possible in the lungs, for Nature has provided a catch-pit and filter by means of the nostrils and nasal fossæ. In normal breathing the air is drawn equally through each nostril, in which the larger particles entering with the current are screened off by the hairs arranged for that particular purpose. Those particles which are finer, and have so managed to pass

through the filter, find themselves within the nasal fossæ, where they are exposed to the action of the mucus secreted there. Now, this mucus has been proved by Messrs. Würtz and Lermoyez to be very distinctly bactericidal, so much so that bacteria which get through without being destroyed are rendered so feeble that they are expelled by sneezing or coughing before they can possibly effect a lodgment.

Now, we know that the function of a part is impaired or lost by disuse; hence young people, who habitually breathe through their mouths from the presence of adenoids, etc., do not secrete this bactericidal mucus; wherefore the pharynx in such cases is no longer protected by the overflow of this bactericidal mucus, as is normally the case, but receives the air impinging upon its unprotected surface at whatever temperature the atmosphere may chance to be, and laden, it may be, with impurities of all sorts. Can we, then, wonder that phthisis is so common in young adults? But why do they keep their mouths open? Take a glance at the faces of the phthisical, note the pinched nostrils, the high cheek-bones, the prominent teeth, and draw conclusions. Let us look into their ears and see the retracted membrana tympani. Let us look up their nostrils and see the projecting inferior turbinated bones or curved and thickened septum. Let us pass our fingers behind the velum palati and find the adenoid growths there. I do not say that every phthisical patient presents all these symptoms, but nearly all manifest some of them.

Such conditions give rise to continual coryzas, sore throats, and constant attacks of bronchitis, which keep the mucous membrane of the lower air-passages in a state of chronic irritation; it follows, then, that by this increased vascularity thus engendered the system is more open to attack.

Another cause of infection by inhalation is by particles of the straw which is laid down in our streets to deaden noise; this becomes quickly contaminated by germs of all kinds, is

ground small, so that particles are wafted, with deadly germs clinging to them, by the eddying air, to find a home in some poor unfortunate animal, human or otherwise. There are other predisposing causes to infection by inhalation ; we would call attention to the fact, now well known, that phthisis is much more common in certain districts and in certain occupations than in others, the one sometimes depending on the other, for it frequently happens that certain trades congregate round certain localities, such as cutlery at Sheffield. Now, in the trades of knife-grinding, needle-grinding, stone-masonry, colliery work, etc., particles of exceedingly irritating dust are constantly being inhaled, leading to minute woundings or abrasions of the air-passages and lungs ; even particles of cotton, clay, straw, or flax, may produce the same result, the effect being that the tubercle bacillus can make a lodgment on a freshly abraded surface, and so obtain a foothold. A somewhat similar condition may be produced by the excessive cell proliferation and denudation of the mucous membrane provoked by such diseases as measles, diphtheria, and scarlet and typhoid fevers.

Whatever may have been the predisposing cause, the line of infection follows the course of the lymphatics, causing a local lymphangitis, which, if followed by an abundant leucocytosis, may even then arrest the bacillus in its attack ; if not, the bacillus pursues its way along the lymphatics. We know how these lymphatics are in relation with the serous membranes : that those of the naso-pharynx are intimately connected with the meninges of the brain by the perivascular lymphatics ; that those around the trachea are in connection with the upper cul-de-sac of the pleura, which explains the reason of the frequent occurrence of tubercular meningitis in infants, and why the base of the brain and apices of the lung are attacked in young adults in whom the lymphatic system is much developed. If, however, the infection has been due to direct inhalation into the lung itself, and not by means of

the lymphatics, the result is somewhat different, for the apices in this case are not more affected than other parts of the lung. Especially is this so in the bacillary broncho-pneumonia of early childhood.

In this form of infection by direct inhalation, tubercles are formed in the lungs themselves, which become still further affected by particles of tuberculous matter falling or being drawn into the infundibula of the lower part of the lung, instead of being expelled with the sputa. In a healthy mucous membrane the cilia soon get rid of tubercle bacilli which may have accidentally intruded, so no harm results ; but in cases in which the cilia are wearied and overtaxed by constant irritating particles, which sometimes even tear them from their cells by their roughness, they either no longer attempt to cope with the bacillus, or the bacilli may drop into the place left raw by the wrenching away of the cilia. In regard to tubercular laryngitis, the probability is that it is due, not to direct inhalation of the bacillus, but from the resting upon the larynx (already irritated by the various modes mentioned) of sputa which are loaded with tubercle bacilli in a state of virulence from an already infected lung, even though there may be no stethoscopic signs to reveal its presence. Probably, therefore, tubercular laryngitis is never primary.

From the foregoing remarks upon inhalation, it may be seen how exceedingly necessary it is to attend to the freedom of the naso-pharynx in children and to the personal hygiene of those passages in any adults who are in any way exposed to phthisis.

3. Infection by Ingestion.—That this may occur can very easily be proved by experiments with guinea-pigs ; indeed, some of those that had been used in the laboratory in Paris, to ascertain the effects of pure yeasts as remedial agents, were rendered tuberculous by mixing with their food both pure cultures of the bacillus and sputa from well-marked cases of human tuberculosis. Ingestion is a very frequent

form of infection amongst children, whose diet so largely consists of milk, and it is a terrible thing to contemplate that such an enormous number of milch cows have recently been found to be suffering from tuberculosis, as it is from tuberculous disease of the udder infecting the milk that tubercle is conveyed from the bovine tribes to man. Fortunately these animals do not cough and expectorate sputa laden with bacilli.

Tubercle is very seldom, or never, communicated to man by means of the meat of tuberculous animals, the bacillus being killed and destroyed by the heat used in cooking, even should it be present in the muscles of the animal, a phenomenon hardly ever seen; therefore boiling the milk is a safe way of destroying the vitality of the microbe. Children, however, do not, as a rule, care for the flavour of milk that has been boiled, hence this valuable precaution is often omitted by indulgent parents and nurses. This objection may be entirely obviated by sterilizing the milk in a very effective and cheap sterilizer made by Down Brothers, which retains all the flavour of the milk.

The stomach is a first-rate protector, even in cases in which tuberculous milk has been ingested, for it destroys most of the bacilli (though probably not the spores); those escaping, not being in a very vigorous state, are hurried through the intestinal canal before they have had time, or have acquired power, to effect penetration. We may also remark that the tubercle bacillus is one of the aerobic kind, requiring free oxygen for its development. Now, the intestines are a locality where this is very unlikely to be met with. In food, however, and in the extraordinary things that children put into their mouths and swallow, there are found many substances likely to scratch or injure the mucosa; and when I say 'scratch,' I mean a microscopic scratch, in which a microscopic being may drop, and either effect penetration by the suction action of the lacteals, or may be seized upon by the nearest

leucocyte, and so introduced into the system. Luckily, it far more often happens that where the scratch has been made, no bacillus has passed until healing-over has taken place. When, however, penetration has been effected, the same process occurs as we have described before, in speaking of other forms of invasion. A local leucocytosis may save the patient, in which case the temporary malady may never be diagnosed, and I imagine that many stomachic disorders of children may be due to this cause. If this saving leucocytosis is absent or insufficient, and the leucocytes get conquered in the struggle, then the bacilli are taken to the nearest gland, as a rule, but not always, owing to the peculiar arrangement of the lymphatics. Arrived at the gland, they are held by that gland for weeks, months, perhaps for years—sometimes, indeed, for ever—the gland or that part of it which is affected undergoing certain changes which will be described later on.

I should here mention that the denudation of the mucosa over and around Peyer's patches from the action of typhoid fever sometimes paves the way for the invasion of the tubercle bacillus, and I am inclined to think, from cases that I have observed, that typhoid patients should never be fed upon milk (the staple food) until previously sterilized, and that this should be carried on well into convalescence.

Finally, there is infection by the ingestion of sputa that are swallowed by phthisical patients; the lesions in this case are definitely new primary infections, and are not by interior conveyance, but by very unnecessary auto-infection. This is especially seen in the tuberculous insane, who have not the sense to expectorate; accordingly, it is thus that we find a much larger proportion of extensive intestinal tuberculous lesions in the pulmonary consumption of the insane, as has been pointed out by Mosler. I am not forgetting that Woodhead has clearly demonstrated that in many cases the intestinal lesion is really the primary one, though the pulmonary lesion may be the cause of death. The two

can be distinguished, and the latter happens when, as I mentioned just now, the invading bacillus is not taken to the nearest gland, but to one of those at the root of the lung, or, at least, one that is connected with it.

4. Invasion through the Genito-Urinary Passages : This has been clinically observed, and cases are rarely reported in the medical journals ; but it is decidedly uncommon, and does not merit that in this work we should give it much consideration.

Predisposition and Heredity.—The latter may easily be disposed of. Formerly, before the true pathology of the disease was known, considered of the first importance, heredity is now only deemed to be a predisposing cause in so far that, as all ferments prefer a certain wort or terrain of growth, certain conditions favourable to their development, so this particular condition may be inherited in the same way as are features, tricks of manner and mind. That the tubercle bacillus itself may be passed on and transmitted from either parent to the offspring is held to be impossible ; it certainly has never been proved, even in animals so susceptible to the disease as are guinea-pigs. The disease may often appear to have been transmitted, when the real infection has been from the close contact of the children with their diseased parents, in the same unfavourable conditions.

As against the doctrine of acquirement by heredity, it is worth while calling attention to Rœckl's remarks that in calves and young animals tuberculosis is rare, but becomes more frequent as the animals get older, especially those which are exposed after birth to an existence in common with diseased parents and amidst infected surroundings.

Not only does there appear to be a certain special predisposition in individuals, but also certain organs of individuals seem to offer a more favourable terrain for the growth of the tubercle bacillus than others, and these may vary according to the age of the individual.

The history of the bacillus, after it has affected penetration and overcome the local resisting forces, we have traced to the nearest (usually) lymphatic gland, or to serous membranes by their connection with the lymphatics, although no explanation can yet be given as to means by which a non-motile bacillus is able to progress against the stream. We can now resume the history. When the invading bacillus reaches a gland by its afferent vessel, it is arrested in the cortical substance of the gland by the reticular structure of the tissue, and by the natural phagocytes existing there. At this particular point the phagocytes, which are often, and, indeed, generally, insufficient, for reasons before stated, to cope with a microbe so virulent that it has already passed through the line of sentries, band together and act as supports to check the invader on a second line of resistance. This banding together or coalition of phagocytes is seen in the formation of a giant-cell. Should this second line of resistance be forced by the virulence of the invading microbe, we find that it penetrates along the lymph sinuses even to the medullary portion of the gland, although by the time it has succeeded in accomplishing this, the lymph sinuses have become completely filled up with inflammatory products, the object being to limit the invasion by the erection of a barrier. This constitutes the reserves or third line of resistance, and is usually sufficient to encapsule the invader or hold it indefinitely in check. Even this third line of defence may be forced after a longer or shorter time, depending upon the vitality of the general system and the special nutrition of the gland. Should this be the case, then the efferent vessel becomes seized upon; this being the high-road to the system, the whole body becomes exposed to the ravages of the invader.

We will turn for a moment to other tissues primarily affected, and not secondarily, as all glands must be, albeit that the primary infection is generally never known. Let us take for example the pleura covering the apices of the lungs, or the

serous membranes (meninges) at the base of the brain. It may be objected that these are also secondary infections, as before shown, from primary infection through the pharyngeal or nasal mucosa. The objection is just, but it would be well to draw attention to the fact that between primary, secondary, and tertiary infections, as well as between first, second, and third stages of the clinical aspect of the disease, there is never any clear line of demarcation. To return, however, to the serous membranes. These structures, when invaded, succumb more easily to the action of the bacillus and its toxins than do the glands ; but in all cases, allowing for differences of structure, the microscopical pathology is the same. First comes the local leucocytosis, with consequent inglobing of bacilli ; this leucocytosis may be exceedingly feeble, and the leucocytes find that they have a task beyond their strength, and many of them die, poisoned by the toxins of the bacillus which they have devoured. This happens more frequently with the neutrophile polynuclear cells, which, although greedy phagocytes, do not possess very powerful diastases in their protoplasm, and are thereby powerless to digest any but very slightly virulent microbes; hence they perish, and are in their turn inglobed, together with the bacillus contained in them, by the large mononuclear phagocytes, which have a much slower power of phagocytosis ; but what they lose in speed they gain in power, for their protoplasm contains very powerful diastases, quite capable of digesting virulent bacilli and neutralizing their toxins without any additional help. This may be ascertained by noticing that the bacilli when inglobed swell up, lose their distinctive shape, and become brownish in colour, looking very much like a lightly-cooked sausage. Now, these particular appearances can never be obtained in any preparations made from cultures either living or dead. It is only fair, then, to consider such phenomena as due to the phagocytic and digestive action of the neutrophile cells. Leucocytes are unlike amœbæ in one respect, which is, that

when they once take in a solid particle, they never eject it as long as the life of the cell remains. Koch's bacillus is so poisonous that it usually takes more than one phagocyte (the wandering or fixed) to destroy it; therefore two or more combine together, and so form a giant-cell. These giant-cells may be thus composed entirely of leucocytes or entirely of connective tissue (epithelioid) cells, or even by a fusion of both kinds; a fourth source may be from endothelial cells. I think it may generally be accepted that a giant-cell may be produced either by fusion of cells, as just mentioned, or from a single cell, by excessive karyokinesis without cell division, though the former is the more common mode in the disease under consideration; some observers are inclined to view the former as cell success, the latter as cell failure and degeneration. In cases in which the giant-cell is entirely formed from either the epithelioid or the endothelial cells, it is usually because one of the earlier polynucleated phagocytes has inglobed a bacillus, and has wandered off with it inside to digest it in some quiet corner; but, like a dog that has swallowed poisoned meat, it languishes and dies in that corner; then the neighbouring epithelioid or endothelial cells, as the case may be, set themselves to work, band together to inglobe the whole, and prevent further mischief ensuing. The formation of the giant-cell is the first stage of tubercle.

A fight and struggle now goes on inside the giant-cell between its diastases and the toxins of the bacillus or bacilli, for frequently there are more than one. There may be more than one giant-cell; others may be contiguous, in which case they will be found to anastomose by slender processes, through which their protoplasm can flow to aid each other. Around these giant-cells are found large mononucleated cells, either epithelioid or large mononucleated leucocytes—that is to say, full-grown lymphocytes; it would be hard to say which they are, neither does it very much matter, as they are there for the same purpose, which is to surround the giant-cell, to

watch the fight, and neutralize by their own diastases any of the toxins of the bacilli within the giant-cell which might escape. This is the second stage in the formation of a tubercle.

Beyond these big cells is gradually formed a crowd, layer upon layer, of smaller or lymphoid cells, which are simply youthful leucocytes possessing some power, though little, of secreting alexins and so aiding the fight; but as they possess no phagocytic properties as yet, they are stationed as far from the enemy as possible. There is no particular limit to these cells; there may be many layers of them or few; they are usually contained in a sort of reticulum, or network, but not always, this being much more marked in chronic cases than in rapid ones, which is exactly what we should expect.

Here, then, are all the elements of a gray or recent tubercle, those gray tubercles which are plain to the naked eye being nothing more than a conglomeration of single tubercles, which essentially consist of

1. A giant cell or cells, connected by branches in which lie the epithelioid cells.

2. A layer or layers of these epithelioid cells, possessing both phagocytic and neutralizing powers.

3. A layer or layers of lymphoid cells with no phagocytic powers, but with a certain amount of neutralizing properties according to their age, these being kept in position by a reticulum more or less developed, according to the length of time that the lymphoid cells have been mobilized.

Nothing in this world is stationary—there is either progress or retrocession. The latter will be taken first, as it is the rarer, and will therefore take the shorter time. By retrocession, of course, retrocession of the effects of bacillary invasion is intended, the decline of the disease caused by its advent, and this reversion to pristine or approximately pristine conditions may be brought about in two ways—by a

fibrous or fibroid change, and one that is cretaceous, called calcification.

I. *The Fibroid Change.*—In this case the bacilli are destroyed and digested by the giant-cells, which, exhausted by the struggle, then enter into fatty degeneration—or a species of coagulation necrosis—and are more or less completely absorbed, the fatty molecules being passed on from the nearest epithelioid cells, through the next layer to the lymphoid cells, and so finally eliminated. The connective-tissue cells lying within the branches of the giant-cells and those of the innermost layer of epithelioid cells elongate, branch, and finally form connective tissue, which contracts upon the débris of the fight and forms a scar ; the outer layer of lymphoid cells is replaced by fibroblasts. Lung cavities of any size may heal by the scar tissue lining its walls, which become smooth, and are finally found lined with a membrane ; the smaller cavities always contract, and larger ones may do so after a time.

II. *The Calcareous Degeneration, or Calcification.*—This is somewhat rare, and can only take place in certain constitutions, especially those gouty and rheumatic, in which the progress of the disease has been slow. Sometimes it unfortunately happens that, when a local trouble is being closed in this way, the whole process is interrupted, and, indeed, prevented by an intercurrent acute attack from another source. The microscopic pathology of calcification is that a certain amount of caseation (to be described later on), indicating that the tubercle bacillus has prevailed, has taken place, but that the second layer now brings a new force to bear, that of increased alkalinity, which neutralizes the acid products of the bacilli, thereby causing the deposition of the carbonate and phosphate of lime. This is exactly analogous to the manner in which certain nematodes are encapsuled by the leucocytes, successive layers being deposited by them around the invader, which also protects itself from destruction, as far as it can, by a thickening of its enveloping membrane ; the

bacillus acts likewise, and enters into a state of sporulation, remaining encysted in the alkaline carbonates and phosphates. If this change should occur in a cavity of the lung, it may so happen that the whole thing may be suddenly got rid of by expectoration, in the form of a pneumolith, the cavity then healing by cicatricial tissue.

These are the two processes by which injury to the economy by the tubercle bacillus may be arrested.

Progress of the Bacillus.—If the bacillus should be in a sufficiently virulent state, it gains the upper hand ; first the giant-cell becomes necrosed, then the surrounding cells, which results in the formation of a caseous mass (yellow tubercle). This may be due not only to the virulence of the bacillus, but to the fact that when it has overcome the resistance of the giant-cell, after a long struggle, it finds the surrounding phagocytes in an enfeebled condition, having been for some time cut off from their supply of nutrition, hence the caseation spreads from centre to periphery ; even then it sometimes happens that the third layer has come to the rescue, and has formed a capsule which arrests the disease for who shall say how long ? it is certainly always an element of danger : the cyst may break down at any time and infect the whole system. Should encapsulation not take place, the process continues in the tubercle, and leads to the death of all the cell elements therein, with subsequent softening, caused by the dissolving power over the tissues possessed by the toxins of the bacillus, which still retains its virulence. As softening takes place, the virulent bacillus is free to proceed elsewhere by any channel open to it, or simply by contact with the surrounding tissues leads to their destruction. Thus cavities in the lungs are formed, the softened contents being poured into the neighbouring bronchi. The bacillus continuing to obtain the mastery, and being doubtless often reinforced from without, finally causes systemic death, both by the extent of local lesions and by its teletyptic action of causing solution of

tissues at a distance by the toxicity of its products or toxins.

Tubercle in any part of the body is characterized by these phenomena, modified only by the structure of the particular tissues affected. It will form no part of this work to enter into any description of tubercle affecting the meninges, glands, mucosa, skin, bones, or joints; the only tubercular disease here taken by itself is the one most commonly met with — tubercle of the lung, pulmonary consumption, or phthisis—in its clinical aspects. Phthisis ($\phi\theta\acute{\iota}\omega$, I waste away) may be acute, subacute, or chronic.

Acute Phthisis is rare as a primary disease, but is far more often seen as the result of the breaking down of a gland full of a soft, creamy substance, containing living bacilli in a state of great virulence, and the consequent infection of the system generally, acute phthisis being very seldom unaccompanied by acute tuberculosis elsewhere.

As regards the latent period of this disease, we have not much evidence upon which to form an opinion; it is probably very short. The complaint runs the course, and presents all the phenomena and symptoms, of a true zymosis. It is ushered in with constant attacks of shivering, alternating with sweats, rapid breathing, quick pulse, a short, sharp cough, with a certain amount of dyspnœa, and pain in one or both sides of the chest. The temperature is high, and the skin soon becomes of a very peculiar dry, burning character that I have only seen in one other disease—typhoid fever: it is a symptom to which I attach great importance. The weakness is extreme; the tongue is dry, and very red at the tip and edges. The fever soon assumes the hectic type, delirium supervenes, sordes appear on the lips and teeth, and, as there is generally diarrhœa, the diagnosis between this disease and typhoid fever is at times an exceedingly difficult matter. Crepitation can be detected all over the lungs, but it is not the very fine crepitation of pneu-

monia; dulness or a subdulness is found all over the lungs, in no one place in particular; the cough increases, and there is expectoration of an opaque and purulent kind. There is never hæmoptysis, though sometimes the sputa may be slightly rusty in colour. The patient wastes rapidly, and death may occur even within the first week, or not until the tenth or twelfth.

In cases of early death only gray tubercles are found, which are larger and softer than those before described, consisting chiefly of alveoli filled with epithelial cells and small lymphoid leucocytes within a wall thickened by infiltration with still smaller lymphoid cells. There are no giant-cells in the centre, for there has been either no time for them to have been formed, or it may be that the toxins have been so powerful as to counteract any attempt at phagocytosis. Cases that die later present the phenomena of the harder, smaller gray tubercle, with some of the softer kind, in which giant-cells may be found: in these cases there has been a greater resistance of the natural defenders of the system. In cases that die much later, or about the tenth week, yellow tubercles and caseation are found.

The acute form of phthisis has been divided into several subdivisions, but it will not serve the purpose of this book to enter into them.

Subacute Phthisis.—This form may commence subacutely, or it may come on from time to time during a chronic attack, either from fresh infection or extension of the original deposit. If the contents of a broken-down gland are of very small amount, the resulting systemic effect may not be more than subacute.

Chronic Phthisis.—This is the form in which tuberculosis is generally most apparent, against which so many remedies have been vaunted, for which so many climates and regimes have been advocated, and yet in which so much disappointment has resulted. Cases have been known—cases of

phthisis without any doubt—which have been arrested at least, or even cured, in the past few years, especially since the value of hygienic principles has been recognised, and more especially, too, since the real nature and cause of the disease has become definitely known.

Symptoms.—Phthisis, for the sake of convenience, has been divided into stages, with different pathological conditions and symptoms resulting therefrom, pertaining to each. First comes the stage of invasion, with the consequent formation of hard gray tubercles ; secondly comes the stage of softening and caseation of these tubercles, now become yellow ; and the third and last stage is the breaking down of the softened tubercles, the pouring of their contents into the bronchial tubes, leaving cavities from destruction of the lung tissue, and bringing death from various causes, such as apnœa, thrombosis, exhaustion, or, in rare cases, pneumothorax, when the pleura is not adherent.

As has been said before, it must not be supposed that these three stages are separated by any clear line of demarcation or by limit of time ; for although the first stage must always be the commencement, it happens that when this particular stage is passing into the second, a fresh tubercle may be beginning, and when this in its turn has passed into the second stage, the first tubercle is passing into the third.

Symptoms and Signs of the First Stage.—Cough is the symptom first noticed, though it may have been preceded by disorders of digestion. This cough is more or less persistent, gradually becoming more troublesome, and accompanied by expectoration of a mucous character, chiefly in the morning ; the patient begins to get thin, and finds more difficulty in surmounting hills than formerly, though this does not seem to the patient to be due to shortness of breath, but to fatigue or want of condition. The digestive powers are disturbed, and there may be loss of hair and colour ; generally, also, the temperature from six to seven o'clock in the evening will be

found rather higher than normal, and in the morning somewhat lower. In females there is often disturbance of the monthly functions, which may gradually lead to suppression.

The physical signs in this stage are, like the above, all due to irritation of the lungs, caused by the presence of tubercles; consequently the signs vary with the amount of deposit, tubercles near a serous surface giving rise to more irritation than those in the thickness of a lung. As the infection in the adult almost invariably commences in the apices, it is there that we shall find the first and earliest symptoms, though they do but vary in *degree* from normal sounds, and are so often passed over by the ear that is somewhat out of training. It is always well to seat the patient with the chest bare in a good light, and cause him to breathe rather deeply but softly, as one in sleep. By examining the chest with the eye, first on one side and then on the other, next over the shoulders, we can get a very good notion of the rise and fall of the chest, also whether one side limps a little under the clavicle, or if undue hollows appear above either of them on inspiration. Any limping need not be due to adherent pleura yet; it may merely mean that there is a tender spot, which is eased by the ribs above it taking care to move cautiously. Over such a region there will be more or less dulness, which in some persons is rather difficult to obtain, owing to the irregularity of the deposit in the lung. The breathing is of a distinctly wavy or jerky character, accompanied by a prolongation of the expiratory murmur, with a coarse crepitation, the vesicular murmur tending to a sound resembling that of inspiration. Vocal resonance is slightly increased, and fremitus also. Should any disease exist on the right side of the chest, then the sounds of the heart will be more plainly heard than normal, owing to increased conduction from commencing consolidation. A dry friction sound may often be heard in the suprascapular region, owing to tubercle on the pleura, and sometimes I have found this to be the only

physical sign present. It is present when the serous membrane has been infected through its connection with the lymphatics, probably before the lung itself is invaded. Evidence has recently (*Lancet*, October 23, 1897) been brought forward to show that all pleurisies are due to tubercular infection and irritation.

Another sign often seen in this early stage of subacute infections is a thin red line on the gums next to the teeth. The respirations also are certainly more shallow than normal, and somewhat increased in frequency. In this stage, too, it sometimes happens that an attack of hæmoptysis is the first sign that draws the patient's attention to the fact that there is anything the matter with him. This sign may occur together with very few others, but in young adults, hæmoptysis, unless it can be definitely shown to be due to another cause, is almost invariably due to the infection by tubercle. I think all physicians can call to mind without much difficulty cases of early consumption brought to them with the history of hæmoptysis, the cause of which has been attributed to sore throat or sore gums because the physical signs in the lungs have been too slight to be detected. The spirometer in early phthisis is a great help to diagnosis; a very handy and accurate instrument has been invented by B. T. Lowne.

The microscopical examination of the sputa even in this early stage will often reveal the true nature of the disease, though the quantity of the bacilli present bears no relation to the severity of the infection nor the virulence of the bacilli. Ordinary cover-glass preparations frequently do not contain a single bacillus, whereas if the same expectorations are diluted, rendered homogeneous, and placed in a centrifuge, the resulting deposit will yield them.

Symptoms of the Second Stage.—This is the stage of the conversion of the gray tubercle by caseation into the yellow variety, with its subsequent softening. The emaciation of the

patient increases, the cough is much more troublesome, and is of a moister character ; the expectoration changes from a ropy mucous to a more formed sputum of a yellow colour, less aerated, and sometimes specked or streaked with blood. The temperature is usually raised in the afternoon, though not invariably, hæmoptysis may take place, general weakness increases, and night sweats occur. The sclerotic of the eye appears very white and pearly, whilst the eye itself assumes a pathetic look. Diarrhœa may or may not occur, but is more usual towards the end of the second stage ; to obviate this, the patient should never permit himself to swallow his sputum. The digestive organs become irritated, the appetite capricious, and the tongue often sore ; the nails also show signs of clubbing. The physical signs are : increased dulness over the infected area, with very decided fremitus ; the vocal resonance amounts to bronchophony, or even pectoriloquy, whilst the breathing is of blowing, tubular character, accompanied by coarse crepitation, clicks, and sticky sounds. We now find flattening and immobility below the clavicle. The microscope shows us Koch's bacillus in decided quantities, pus globules, and elastic fibres of lung tissue. At the end of the second stage other microbes are found as the third stage approaches ; these will be presently described.

Symptoms of the Third Stage. — The yellow, softened tubercles are now giving way, and bursting into the smaller bronchial tubes, leaving a cavity behind, the contents of which are constantly being renewed by the ulceration of its walls, and are then coughed up in the form of greenish, lumpy, nummular phlegm. The wall of the cavity may ulcerate through into another neighbouring cavity, the two finally becoming one large cavern. Sometimes, when near the surface of the pleura, and adhesive pleuritis has not previously been set up, a cavity may ulcerate through into the pleural sac, causing pneumothorax. This constant process of ulceration and destruction naturally gives rise to increased cough, with

dyspnœa, more hectic fever and night sweats, which now become colliquative. The emaciation and feebleness increase, the pulse has a running or hurrying character; diarrhœa is frequent and distressing; the feet swell, and the nails, now of a very characteristic shape, turn blue; the tongue gets red and tender, aphthæ frequently form in the mouth, and albuminuria often appears. Cramps and pains in the limbs are frequent, with much general prostration. The patient can find no position that is comfortable; constant cough and expectoration banish sleep; but the intellect remains clear, until the patient is finally worn out and done to death by the action of the bacilli and their products.

The physical signs are, in addition to those of the second stage, which become more marked as the disease goes on, those of cavity: the chest is seen to be flattened and immobile beneath the clavicle, and the ribs appear to be very prominent, owing to the sinking in of the intercostal spaces. If a cavity be empty, we should naturally expect to get a greater resonance on percussion, yet the reverse is almost invariably the case; the dulness is marked. This arises from the wall of the cavity being thickened with the products of inflammation, and surrounded with infiltrated or consolidated lung. At this stage we may get a peculiar sound, called the 'cracked-pot sound,' made by percussing sharply over a cavity whilst the patient keeps his mouth open. Even when cavities are quite close to the surface, I doubt that we ever get increased resonance, unless, of course, there should be pneumothorax. The stethoscope gives us some valuable signs, however, and these are more or less distinct as the cavity is superficial or deep-seated. We may, however, be deceived even in these, for a piece of consolidated lung may conduct all these sounds from a bronchial tube to the ear without any true cavity being present at all. The experiences of the post-mortem room seldom corroborate the exact diagnosis as regards cavities, made clinically.

Cavities, however, may be detected by observing the auscultatory symptoms both before and after coughing—that is, when the cavity is full, partially full, or empty. When full, we may not hear much more than in the second stage (of softening), though we generally get gurgling with sticky guggling noises, or a soft, churning sound, as if a phlegm were being whisked round a cavity, like a stone in a glacier mill. When there is partly air and partly fluid, we may get a splash when the patient coughs or is shaken, or if the communication between the cavity and the bronchus be narrow, we may get a metallic, tinkling sound instead of a splash. When the cavity is empty or in the process of drying up, we get the same breathing and vocal sounds as are normally heard over the trachea above the sternal notch. These sounds are called 'cavernous respiration' and 'pectoriloquy.' If the cavity be large, and its walls smooth, we may get amphoric resonance.

The sputa are green, nummular, and of a peculiar faint, disagreeable odour, the coloration being due to the presence of chromogenic bacteria, and the odour due to the pyogenic varieties, *Bacillus fœtidus* especially. We find under the microscope, besides the tubercle bacillus of Koch, the *Bacillus fluorescens putridus*, *Bacillus pyocyanicus*, *Bacillus pyogenes fœtidus*, mentioned above; different pyogenic staphylococci, especially *Albus;* streptococci, *Micrococcus tetragenes* and others, with the pneumococci of Fraenkel.

Such an association shows that the vitality of the patient is lowered to such an extent that resistance is lost to almost any kind of invasion, for although we know that these microbes frequently exist in the bronchial tubes without doing any harm—probably being rendered innocuous by the mechanical and germicidal action of the bronchial mucosa—we also know that they do not get into the infundibula or alveoli in the healthy system. Therefore some share must be assigned to them in the destructive action of phthisis, though

it is difficult to say how great, or of what kind, that share may be.

Perhaps we ought not to leave the subject of tuberculosis without some reference to tubercular disease of the mesenteric glands, or tabes mesenterica, as it was called a few years ago. This disease does not differ in its pathology from that of tubercular infection of other glands. The form of invasion has already (pp. 153 and 155) been described, and the ending is the same as in all infected glands, either by softening, breaking down, and general infection, by encapsulation during the life of the individual, or by calcification. This complaint is only too common in children, and arises from infection by tuberculous milk. As in phthisis so in this disease, the early symptoms are neither many nor distinctive; hence the true nature of the disease is only diagnosed when it is well advanced. The symptoms arise first from disturbance and irritation of the digestive organs, evidenced by enteric catarrh, with frequent colicky pains and diarrhœa, or, at least, unhealthy-looking stools. This may be temporarily checked, not from treatment, I verily believe, but because it is the nature of tubercular disease to attack by rushes, with periods of rest in between. After several attacks of this kind, the abdomen begins to become generally tumid and prominent, sometimes even tympanitic, though not tender even to pressure.

It may be exceedingly difficult to make out the enlarged glands, especially when lymph, poured out by irritation of the glands, has glued the coils of intestines together, and produced that peculiar appearance of the abdomen called by the French *carreau*. It looks just as if the child had a distended air-cushion of an oblong shape underneath his skin. The patient gets anæmic and emaciated, whilst appetite simply does not exist. The administration of chloroform, with palpation, advised by Jenner, will sometimes prove the presence of enlarged glands, but the absence of this sign must not make us think that we have simply to deal with a chronic enteric

catarrh. Hectic fever eventually sets in, with increasing debility, and ascites often ends the scene.

Careful search should always be made for the tubercle bacillus in doubtful cases. It is exceedingly difficult to find in the fæces, but perhaps better means of search in the future may reveal its early presence. There is one sign to which I attach great importance, and that is the presence of indican in the urine. I have never seen a case of tabes mesenterica in which this sign has been absent.

CHAPTER IX.

TREATMENT OF TUBERCULOSIS.

Tuberculosis, in whatever shape or form it may present itself, is essentially a wasting disease, hence the attention of physicians was early directed to the object of keeping up the strength of the system, both by the administration of tonics and by diet. Of the former there was a large choice, but the latter was the most important, and is just as important now in the treatment we are recommending as ever it was under the old methods. Next in importance to diet comes personal and general hygiene, to which so much attention has been lately so properly devoted, and upon which so much that is good and excellent has been written recently, that it need not be recapitulated here. Following hygiene, and to a certain extent belonging to it, comes climate, a very important consideration for the invalid who has the means, and is able to travel. The various climates and the class of case that is likely to be benefited by them are all detailed in books dealing with those subjects, which as regards our treatment are simply adjuncts. All that I have to add here is a word of warning to those who rush abroad without any precautions and few directions, expecting to feel well soon after reaching their destination, and are very happy-go-lucky concerning any regime. Some cases of early phthisis actually do get well under these conditions ; the change of scene, the warm air and glorious sunshine, give a stimulus to the system,

which enables its defensive powers to effectually put down the invader.

But the air is not always warm, nor conditions always favourable, and there is another side to the picture: an enormous amount of discomfort is often experienced by invalids in a foreign clime, who sorely miss the good, wholesomely-cooked English food—and I say wholesomely-cooked advisedly. I may also say well cooked; for although the English by no means excel in the finer branches of cookery, yet there is no foreigner who can cook a joint or boil a potato as can the English.

Variable as our climate is, after all is said, it is not a bad one. It produces the healthiest, hardiest race in the world. We certainly need more sunshine, we could do with less fog; but we escape the fearful relaxation of the sirocco and the biting cold of the mistral. We have far more good days than bad ones; there are very few days unfit for an invalid to venture out for a short time, and if kept indoors, where in the world can a better interior be found than in England? The great mistake we make is in not warming our corridors and passages sufficiently; but on the American continent and in our possessions there, this is carried to too great an extent.

For those not well off, surely it is better to remain in a comfortable English home than be relegated to a single small bedroom at the top of a hotel—all that many who go abroad can afford—with the use of the public rooms crowded with consumptives in all stages, mutually infecting each other afresh—truly a Bacillary Bourse. I look forward to the time, not far distant, I hope, when by the aid of the pure ferment treatment invalids need go no further away from home than the dry cliffs of our southern and south-eastern coasts, or, for those with whom the sea does not agree, some of the inland hilly regions or elevated beds of gravel, especially among the pinewoods of the Bagshot sands; not huddled together in an expensive but insanitary hotel, but dwelling in parties of four

or six in separate pavilions, the cases being selected according to stage of disease, and the pavilions being scientifically disinfected at regular intervals. The unfolding of the complete scheme must be the subject of a future work.

After the two former considerations follows medicine. Perhaps some might think that this should come first. Formerly, and until quite recent times, the only use of medicines, in addition to promoting the strength, was to allay symptoms as they arose—in fact, to ease the patient's downward path and make it as little distressing to him as possible. Cod-liver oil was the very best of all the medicines then given, but this may really be regarded more as a food than a medicine. All palliative medicines, such as opium, codeia, etc., are well known, so that it is not necessary to discuss them here. Since the true nature of the disease has become known, splendid work has been done and many good results obtained from administrations of such germicides as are not poisonous in ordinary doses to the animal economy; creasote, guaiacol and its carbonate, menthol, thymol, izal, etc., have all been used with some benefit. A distinct step in advance was made by the intratracheal injection of some of these substances dissolved in parolein. Finally, subcutaneous and intrapulmonary injections have been devised and practised, chiefly at Ventnor, by Dr. Sinclair Coghill, with a certain amount of benefit, though the proceeding is painful, and not without risk in inexperienced hands. Ichthyol, too, has been given by the mouth, and thiosynamin by injection, but the results of later experiments do not bear out the good opinion formed of them by their introducers. All of these treatments have the same object in view, that of destroying the bacillus, none of them being intended to aid the system in its own means of resistance. Nevertheless, good results have been obtained for a time; sometimes this *time* has just enabled a sufferer to rally up his own powers of resistance, and so amelioration has been the result. The following is a case in the author's own

practice. The patient returned in June, 1896, from a voyage to Australia. The original disease (tubercular deposit in the right lung) had advanced considerably, and bronchial râles were to be heard all over both sides of the chest, but only dulness on the right, where softening was commencing ; the voice was husky, and talking an effort. I immediately took him to Richard Lake, who diagnosed abrasion with commencing ulceration of the larynx, and, in order to prevent virulent bacilli from lodging upon the abrasion, there and then administered an intratracheal injection of a drachm of izal (1 per cent.) and parolein. This treatment I persevered with at first every day, then every other day, gradually lengthening the interval until September, when the patient, then nearly well, went to Biarritz, where the same treatment was continued. By the middle of October the larynx was completely healed. All these treatments, however, have a great disadvantage, which is, that after a time they interfere with the proper functions of the cells, which suffer from a prolonged course of antiseptics, and consequently lose much of their functional power. It therefore happens that the moment the antiseptics are left off the bacilli again make headway, for which reason these remedies should not be persisted in too long.

Another attempt to cure tuberculosis has been made by injecting the toxins of the tubercle bacillus in minute doses into the system. This was called the ' tuberculin treatment,' and its disastrous results are matters of the recent medical history of our own times. The treatment finds some advocates even now, and upon the value of this treatment, judiciously applied, the reader is referred to a valuable paper by Dr. J. Whittaker, of Cincinnati, published in the *Lancet*, October 16th, 1897, also a communication by Grasset and Vedel in the *Semaine Médicale*, February 26th, 1896.

In the spring of 1897, Koch brought out a new tuberculin, which consists of a solution of the intracellular toxins of the

bacillus. The treatment has been fairly well tried in England, in spite of the unscientific reasons for its application, and the general opinion seems to be that, although it does not do positive harm, there are few, if any, good results from the treatment. To this statement exception must be made to some remarkably good results obtained by Malcolm Morris in cases of lupus, communicated to the *British Medical Journal* (July 24th, 1897); after a period of six months, several of these cases have gone back. Another of these toxins is a deutero-pepton, prepared by Klebs, which he calls 'anti-phthisin'; it is spoken of very hopefully by Carl von Ruck, but others do not seem to have had the same success with it as he claims to have had.

The antitoxin or serum treatment has not made much progress, and for this reason, that there is no warm-blooded animal that is immune to tuberculosis, therefore a true anti-toxin cannot be obtained. Maragliano has prepared a serum which deserves a certain amount of notice; it is prepared by mixing three parts of the intracellular poison of the tubercle with one part of its products, or extracellular toxins, thus forming a mixture of the original and new tuberculins, the extracellular toxins being, according to Maragliano, extracted from extremely virulent cultures. But the author does not tell us how this virulence is obtained, which is to be regretted, as the chief difficulty bacteriologists have found with this bacillus is the seeming impossibility of either exalting or attenuating its virulence. Of this mixture of toxins 2 cubic millimetres are injected into horses, asses, or dogs (animals refractory to tubercle); this dose is increased by 1 cubic millimetre per diem until 40 or 50 cubic millimetres (according to the weight of the animal) are injected, and this dose is daily injected for six months. A high degree of immunity is thus produced, and the serum is then drawn off from these animals in the usual way and preserved. It has been tried in human tuberculosis, with improvement in some cases that have not been far

advanced in the disease. Experiment shows that Koch's bacillus will not grow in this serum, but this does not prove very much, as, conversely, the diphtheria bacillus will grow very well in the antitoxin serum for that disease, which is powerful in checking its action in the human body when injected sufficiently early. It is possible that Maragliano has modified the views he expressed in 1892 (*Berliner Klin. Wochenschr.*), that the symptoms of phthisis were due more to associations or symbiosis of microbes than to Koch's bacillus. If this is so, I think the change of opinion is in the right direction.

I have now mentioned most, if not all, of the attempts at cure, founded upon modern ideas, of this intractable disease; but all possess one great drawback (climate and open air excepted), and that is, that they are more directed to the destruction of the bacillus within the system, than to aiding and reinforcing the natural defences of the body.

I will here quote the words of wisdom made use of by Dr. Edward Squire (*British Medical Journal*, January 25th, 1896): 'The best means we have for destroying the tubercle bacillus within the body exist in the action of the *living cells and fluids* of the body—the natural safeguards against deleterious germs. If we drench the tissues with antiseptics, we may diminish the vitality of the bacilli, but at the same time we impair the vitality of the "phagocytic" cells, and this not only at the disease centres, but throughout the body' (the italics are mine). These words express clearly what the true line of treatment should be. This true line is also recognised by Dr. Oscar Liebreich, who proposes to carry it out by injecting two different substances into the system, which, when they meet within it, unite to form another substance, inimical to the bacilli and stimulant to the phagocytic and alexin-producing cells of the body. The substances employed by Liebreich are myrosin and potassium myronate, which are perfectly harmless in themselves, the

latter possessing a feeble antiseptic power, nothing more; yet when these two are mixed, in the presence of a fluid, a new compound, allyl sulphocyanide, is formed, which possesses very powerful antiseptic properties, but does not readily combine with proteids, and therefore does not interfere with the functions of the cells within the body. The two substances are injected in different places and at different times, so that the formation of allyl sulphocyanide in the tissues of the body takes place gradually as the two substances happen to meet, and occurs in such minute quantities in any given place that its otherwise exceedingly irritating property is reduced to a minimum, whilst the antiseptic action of the nascent substance is the more powerful. The results were certainly favourable upon tuberculous guinea-pigs, especially upon the spleen. This treatment has not yet been tried upon man, so we cannot say how the process may affect the sensations of the patient. It may be exceedingly painful, but, unfortunately, the poor little guinea-pigs cannot express their sense of suffering; and I have my doubts about the correctness of the view that the action of the natural safeguards is stimulated.

If we now refer to Chapter VII. of this work, we shall be reminded that in the life-history of the yeast cell within the body we have certain chemical bactericides, alcohol, etc., thrown into the system in a nascent state, therefore fulfilling the aims of those who rely upon the antiseptic treatment only. We see also that the nucleins contained in the yeast cells are almost identical with those of the human body, and, like them, they are capable of secreting spermine or alexins, thereby aiding the natural safeguards of the body by using exactly the same weapon and the same ammunition, thus carrying out the objects of Squire's remarks quoted above.

Furthermore, we have seen that these yeast cells, under certain important conditions, have a very decided phagocytic power, and that they not only assist the natural safeguards by stimulating them with medicine, with food, and with the

moral effect of reinforcement, but they actually make use of means of waging warfare against bacilli in the system, that was unsuspected, even in the leucocytes, until a very few years ago. I have had a most interesting experience of the phagocytic power of yeasts within the system. On September 19th, 1897, a patient, undergoing the ferment treatment, received an injection of backérine in the right sub-scapular region. On October 15th his expectoration was examined. Besides the usual elements, there were a few pus corpuscles, numerous cocci, but no tubercle bacilli were seen in this specimen. M. Lachenaud, who was working this specimen with me, called my attention to a curious object, looking something like a chain of streptococci of enormous size, but unstained, transparent, and of a pale straw colour. I was puzzled for the moment as to what it could be; by raising and lowering the micrometer screw I made out two chains, one partly superimposed upon the other, and then I suddenly recognised them to be yeast cells in the form of hyphomycetes. This is a form which might have been expected from sojourn in the lungs, wherein oxygen is plentiful [*vide* Chapter VI., Experiment IV. (7)]. Close examination of these hyphomycetes showed that the third, fourth, and sixth link of the chain contained within them some highly refracting bodies, bearing such a strong resemblance to Koch's bacillus as to be identical with it. The top link of the underchain also contained a bacillus, and the last link of this chain appeared to have a little tail, which may have been a bacillus lying end on with the cell.

I have never seen yeast cells in this hyphomycetic form before this with bacilli englobed, and I imagine that this is the first time that yeast cells have ever been seen to have passed out through the human system carrying bacilli inglobed within them at their exit. There was no question as to the bacilli being really within the cells, for they dis-



FIG. B.

(HIGHLY MAGNIFIED.)

Yeast cells of the hyphomycetic form, found in the expectoration of a patient under treatment. Drawn to show the liability of an observer to mistake crinkles and outlines of the degenerated cells for inglobed bacilli.

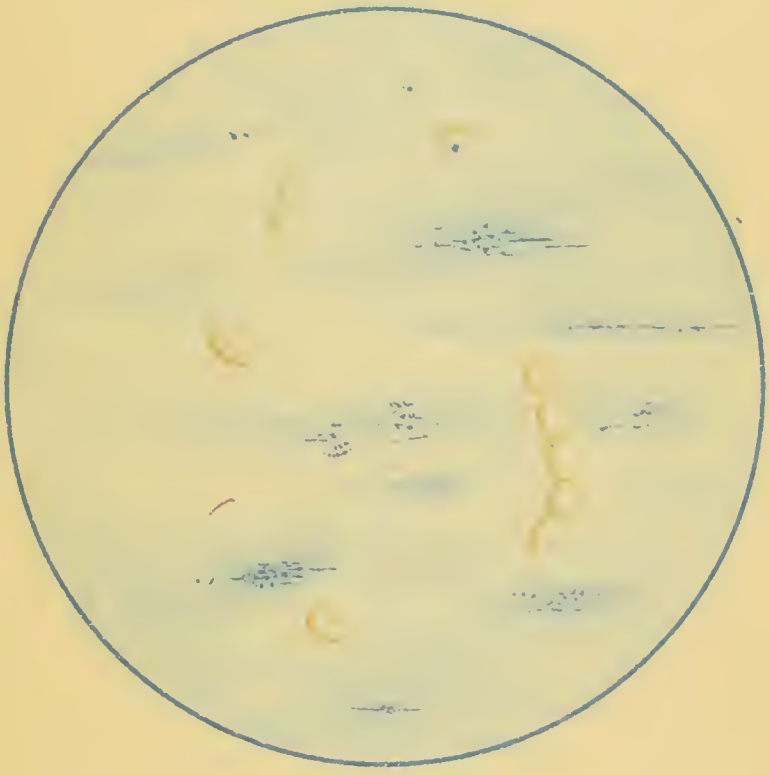


FIG. A.

Saccharomyces Cerevisiæ, from the expectoration of a patient under treatment, containing the tubercle bacillus inglobed. One bacillus is seen lying free; a micrococcus is seen lying above a single yeast cell, and not inglobed within it.

appeared and reappeared equally with the cells when the micrometer screw was turned either way, thereby proving that they lay on the same plane.

I regarded this discovery as of enormous importance, as proving the practical success of that part of the treatment which depends upon phagocytosis. Unfortunately, this particular slide got broken, but another had been made from the same expectoration. In this we found many yeast cells, both of the ordinary oval shape and of the hyphomycetic form. Some of them seemed to contain bacilli, but I think they were only folds in the envelope of the cells. Finally we came upon one conidia with a very evident bacillus inglobed, stained red. Near by was a hyphomycetic chain, the top link of which contained a bacillus inglobed. In the same field were a few other yeast cells, but empty, though in the top part of the field was a single oval yeast cell with a micrococcus lying upon its superior surface, and this was especially useful in serving as a comparison to the inglobed bacillus. Lastly, lying below the single cell containing the bacillus lay a free typical tubercle bacillus, stained a very evident carmine; this was the only free tubercle bacillus we could find in either preparation. A sketch of this field was made with the camera lucida, which I here reproduce, as well as a drawing I made of a hyphomycetic chain from the lung of another patient about two months later. This is more highly magnified, and is drawn to show how easy it is to mistake crinkles in the outside membrane for inglobed bacilli. We not infrequently find yeast cells in the lungs of those under treatment, but it is most rare to find any bacilli inglobed; this may probably be because the yeast cells at the time of their expulsion from the body are beginning to undergo degenerative changes. The red colour of the bacillus will help to distinguish the difference between inglobed bacilli and folds of the outer membrane. Yeasts that have been through the body do not stain well; this is supposed to betoken degeneration. The

slide mentioned above we have still, for future reference, carefully marked and labelled.

Regarding the actual administration of the ferments, I have not much to add to what was said in Chapter VII., p. 128. It would be well, I think, after the first three or four injections, to be careful that the system does not get to rely too much upon auxiliary forces, the object being to reinforce and not effect a substitution, even if that were possible. The best places for injection are the supraspinous regions, the interscapular space, a region near the anterior border of the scapula or posterior border of axilla, also the infraclavicular region towards the mesial line, low down near the origin of the pectoralis major, according to the side diseased. We vary the spot at each inoculation ; should both lungs be affected, then alternate the side. In cases of tabes mesenterica, the left flank near the spleen is the best region, or, if the abdomen is much distended, near the apex of Scarpa's triangle on either side, whence it will soon find its way into the lymphatic stream of the abdomen.

The signs of improvement in phthisis first noticed are increased arterial tension, good sleep, reduction of night sweats (although these always occur after a reaction), lessened moist sounds in the lungs, with general increase of energy. The expectoration becomes more aerated and less nummular, whilst the microscope reveals fewer pus cells and fibres, also fewer strange associated bacteria in the sputum of those in the second and third stages of the disease.

Like all remedies, the ferment treatment is most valuable in the early stage, that of invasion, and before the products of the bacilli have had time to poison the system. In such cases we may confidently expect from 85 to 90 per cent. of arrested disease, if not cures ; usually the arrest is permanent. In the second stage the cure takes longer to produce good results, but those who have been patient and persevering have been well rewarded ; many patients whose livelihood depends

upon their work have been enabled to continue with it during the treatment, but those who can afford to rest get on much faster. It is hard for a delicate girl with chest mischief to go running about and serving in a crowded shop all day, but many do it, receiving their injection on a Saturday night, and are at work again on the Monday. Considering the drawbacks, their progress towards cure is wonderfully satisfactory.

In the third stage so much depends upon the amount of lung tissue remaining between the infected foci. Many such cases improve marvellously, especially if the symptoms of poisoning by the toxins do not predominate. If there is sufficient strength left in a naturally good and unvitiated constitution, even in the third stage, we may expect much, especially in cases of unilateral phthisis, in which one lung can do all the work whilst the other is recuperating.

After an injection the expectoration is often increased, and contains more bacilli; it will be noticed also that these bacilli become sporulated, as if hardening themselves against attack. It really seems as though the contents of the cavities were squeezed out to make room for the healthier products of a granulating surface, and it will be noticed, as the treatment continues, that the expectorations become very much reduced in size.

Naturally, we do not get a sudden restoration to health after one or two injections. We do not expect miracles, neither will they happen, but we shall get much solid satisfaction from the treatment. We have not discovered the elixir of life, but we are introducing what we profoundly believe to be a more rational and natural method of cure than any that has yet been devised. After a few weeks' treatment we shall generally find, on looking back, that our patients are unconsciously doing more, show more inclination to interest themselves in things, are not inclined to retire so early, and feel that they would like to walk a little more and find that they can.

The treatment must be persevered with, but not pushed to extreme. It should be used with the discretion we use when we apply bandages and splints to injured joints. We support them when they need support, but never allow them to depend always upon artificial support; so with the natural safeguard cells, they must not be spoilt and led to think that their work will always be done for them—if so, their energy, at first aroused by emulation and appui, will sink into lethargy, the whole system will suffer and succumb in consequence. Other interesting points concerning personal management, and, above all, diet, must be passed over now and reserved for a future work, this not being intended as an exhaustive treatise on disease.

For experiments made upon animals artificially rendered tubercular, the reader is referred to De Backer's book upon 'The Therapeutics of Ferments,' Tuberculosis, third part, p. 401. Some of those experiments I have witnessed, but have neither repeated nor initiated them. All the experiments *in vitro* mentioned in this book I have verified in my own laboratory.

CHAPTER X.

DIVISION I., CLASS A.—ZYMOTIC DISEASES.

Diseases in which the pathogenic microbe is recognised :

1. Diphtheria.
2. Ulcerative Endocarditis.
3. Typhoid Fever.
4. Malarial Fever.
5. Septicæmia.
6. Pneumonia.
7. Influenza.
8. Puerperal Fever.

The three first diseases will be considered separately and in detail, as I have personal experience of the treatment of them by pure ferments ; of the others I have no personal experience.

In cases of septicæmia, both in its ordinary form and that fatal form which occurs in the puerperal state ; in pyæmia, also, even with its secondary abscesses, the yeast cells are more likely to reach the focus of distribution than any remedy with which we are acquainted, and would certainly destroy the infective power of any emboli which they might meet with in the blood current. In woolsorter's disease, or any zymosis from bacterial invasion, we can well imagine that any remedy which can reinforce the natural defences of the system would be a most appropriate remedy with which to combat the disease ; therefore I should not hesitate to apply this treatment at once in such cases, but, without experience, I must limit myself to calling attention to the fact that the field seems very favourable for careful trial.

Influenza is usually so quickly over, and so little fatal in

the early stages when uncomplicated, that it is probable that we shall not use it much for this, unless the treatment becomes so general that few practitioners will be without a stock of tubes for various purposes. The cells for this complaint will be fed in the same manner as those for phthisis.

In cases in which the influenza bacillus has paved the way for the pneumococcus, we have to deal with a far more serious and fatal disease; therefore the sooner this malignant partnership is dissolved by the destruction of the two microbes and the neutralization of their toxins, the earlier and better chance will the patient have of throwing off his disease and escaping chance of unfavourable termination; especially is this the case with elderly people, who bear the injection and reaction remarkably well, and in whom the good effects of the treatment are most marked.

It is well known that the influenza bacillus very soon dies out in cultivation, and I have good reason to believe that a similar condition occurs within the body. This probably occurs from its products, or toxins, being very deleterious to its own vitality. To avoid complete destruction, it is capable of throwing itself into a state of spore, a property possessed by most bacilli, in which state it preserves a latent vitality, though powerless. The toxins are now quickly eliminated from the body, so that the fluids and humours once more become favourable to the growth of the bacillus, which then emerges from its latent state, proliferates, and causes what is known as a recrudescence of influenza.

It is certain that in many cases the toxins of the influenza bacillus produce a prostrating effect upon the strength of the patient out of all proportion to the initial severity of the attack, and I am inclined to think that the ferment treatment, by neutralizing these toxins, may often restore to vigorous health the poor wrecks that influenza leaves, also that it would entirely prevent this recrudescence, which some unfor-

tunates seem never able to shake off. I quote here an extract from a letter written by Dr. Charlier, of Paris :

'There is one disease against which ferments appear to me to act in a wonderful manner. It is influenza. I have noticed that my patients under injections for tuberculosis escaped influenza in the midst of the epidemic which affected every other member of the family. I have seen some taken with influenza when they have been rather a long time without an injection, but in these cases a single injection has quickly cured them. I have not, nevertheless, systematically treated my influenza patients by injection of yeasts, but I think it should be tried by someone who has a good field for experiment, such as at a hospital.'

These remarks entirely tally with my own views and experience.

DIPHTHERIA.

If I do not in this work give a very prominent place to so important a disease as this, as I have done in previous chapters to tuberculosis, it is not because diphtheria merits it the less, but because in tuberculosis it was necessary to point out the peculiar action of the bacillus of that disease, its different mode of behaviour to any other known, and the reason of the failure of all ordinary treatments, together with the suggestion that the rational auxiliary resistance supplied by pure yeast ferments would be likely to succeed.

In diphtheria, as a general rule, when taken at an early stage, we may safely rely upon the powerful action of anti-diphtheritic serum, the employment of which has so much lessened the mortality of this disease. Great as has been the success of this treatment when compared to any other, still, its general efficacy is not so universally recognised nor accepted as many who have seen one or two cases may think. This has been pointed out by Professor Liebreich and others. A few brilliant successes do not constitute an unfailing

method, for many failures have to be constantly recorded from treatment by antitoxin. These failures may be due to several causes besides the most ordinary one of being too late, such, for instance, as from errors in standardizing, insufficiency of dose, etc. But it is no part of my work to enter into the causes of failure, but only to show that we have another remedy of great potency, and that in cases in which the time has gone by wherein success from antitoxin may reasonably have been expected, even then we need not despair. Recent observations are leading me to the opinion that pure ferments cultivated as for tuberculosis have the power of giving a spur to the system, and so enabling antitoxins to aid in the cure which otherwise would have been too late.

As in other experiments upon animals, the reader is again referred to the work by De Backer, wherein he will find some very interesting observations upon rabbits which received inoculations of cultures of the diphtheria bacillus in the vein of the ear, and which duly recovered under injections of backérine. Here I will record two cases in which the action of these pure ferments was so marked that I believe in the future we shall be able to save innumerable cases, both of those who now die from the initial severity of the attack, and of those who succumb to the after-effects produced by the toxins of the Klebs-Löffler bacillus : for, as already stated, the peculiarity of this bacillus is its teletyptic power—that is, although it is itself very little distributed in the tissues of the body, yet it is able by means of its toxins to set up a necrosing action upon the tissues at a distance from its habitat.

The first of these cases was that of a little girl, aged three years, whose entire symptoms were limited to the nasal and naso-pharyngeal passages as far as could be ascertained. There was never any membrane on the throat, neither were there any croupous symptoms ; all that could be noted was a yellowish-pink, gelatinous-looking discharge, which used to

appear at the nostrils, forming a brownish crust where exposed to the air. The same kind of discharge could be seen descending from the posterior nares. The rhinoscope revealed no false membrane, yet this discharge possessed that peculiar odour that those who have seen much of this disease must recognise, which I regard as pathognomonic of diphtheria, and I have found many experienced nurses who hold the same opinion. To decide the question, a culture of the discharge was made upon a slice of potato dipped in bouillon; this yielded the microbe of pseudo-diphtheria, but not the Klebs-Löffler bacillus. The culture was not made until several days had elapsed. As the ferments in this disease had only then been tried by injection into animals, I limited myself to the local application of ferments mingled with fermentable matters. These had to be made fresh daily, as I was at that time only in possession of a very modest laboratory. This mixture was syringed up the nose, and applied to the naso-pharynx by means of a curved brush. This was repeated several times a day with very great relief to the little patient, so much so that after a few applications she made no further objection to them. At the end of ten days all discharge had ceased, the ferments were stopped, and a weak solution of formalin was used instead. There gradually came on a nasal way of talking, showing some paralysis of the velum. This was accompanied by albuminuria, which in a few days became of very great intensity; the child was very weak, but not prostrated. Ten days later all the albuminuria had finally disappeared; the little girl was brighter and better, with increased appetite. There was, however, slight paralysis of the lower limbs, which soon passed off. I was then called away to the South of France, leaving my little patient convalescent, yet in less than a week the paralysis again declared itself, finally attacking the diaphragm quite suddenly, and causing death from apnœa. I am convinced, from subsequent observation, that had the pure ferments been injected into the child's system the deadly

necrosing action of the bacillary toxins would have been neutralized by the nuclein of the yeast cells. It has been proved in animals, artificially rendered diphtheritic, that a cure has been manifested when ferments have been injected after an interval of time that would preclude any justification of the expectation of success by antitoxin, which, furthermore, is powerless against after-effects.

The second case was that of a lady between fifty and sixty years of age, who complained of sore throat one Sunday morning after a rather uncomfortable night. By the late afternoon the condition of the throat had become so irksome and painful that she sought medical advice. When I saw her about six o'clock, I found the usual symptoms of fever; the tonsil on the left side was inflamed and red (but not dusky red), and upon it appeared numerous small gray patches; the glands on this side were tender, the tongue covered with a creamy fur. Temperature 101·4°; no albuminuria. The diagnosis was not clear, but the case was isolated and treated as one of early diphtheria. The next morning no doubt existed; all the little patches had coalesced to form a membrane, from which, later in the day, the bacillus of diphtheria was taken by a swab. The temperature was now 102·6°, with all the symptoms of the night before increased. The patient felt very ill, and was much depressed. By mid-day I had prepared some backérine from an old culture that was quite pure enough for local use, but not for purposes of injection. This was sprayed liberally upon the throat every two hours, the backérine being kept in a small ballon plugged with cotton-wool, and plunged in ice to prevent fermentation. Until mid-day, when the temperature had risen to 103°, the throat had been sprayed and mopped with a solution (1 in 2,000) of perchloride of mercury; but when the backérine was ready, this was substituted for the corrosive sublimate. The medicine was continued. This consisted of the perchlorides of iron and mercury with glycerine. By the evening the temperature had fallen to

101·6°; all feverish symptoms were lessened, and the appearance of the throat had much changed for the better. The membrane seemed thinner, and the base much less inflamed; the glands, also, were much less painful and tender. The patient expressed herself as much relieved, had lost all her anxiety and distress, took her nourishment well, and seemed inclined to sleep. The next day (Tuesday) I found that the patient had had a very good night, taking nourishment at intervals, and felt quite herself; the temperature was only 99°. The throat showed very little membrane left, though the tonsil looked very raw. Same treatment continued: during the night the throat had been well sprayed before the administration of food. In the evening the temperature was normal, the membrane all gone, and no pain or tenderness in the glands. From this time the spray and medicine were gradually discontinued, and the patient recovered rapidly without any further symptom.

In this case, the probability is that the ferments followed up the bacillary products almost as quickly as they were formed, so that they never got thoroughly into the system; also that the bacilli were engaged with the yeast cells *in situ*, many being destroyed by the phagocytic power of the saccharomyces; for, although prepared from an old culture, I had given them one fermentation in a high temperature, and so roused them into full activity. The superiority of the saccharomyces over the perchloride solution in clearing off the membrane and giving ease and relief to the patient impressed the nurse, who chiefly administered the spray, as much as it did me. This case strengthened the conviction at which I had been gradually arriving, that in these pure ferments we have a most potent and efficacious means of destroying Löffler's bacillus, and of neutralizing its destructive and fatal powers, and this in a manner quite innocuous to the patient.

ULCERATIVE ENDOCARDITIS.

Of this disease I have but one case to record, induced, not by the bacteria which usually cause this disease, but by the bacillus of influenza; and I am inclined to think, from reports that reach me about the deaths from influenza, that this disease follows an attack more often than is generally suspected.

My patient was a man fifty-six years of age, short, thick-set, stout, florid, of more than ordinary muscular strength, and temperate in his habits. He first came under my care, as he had suffered from general liver derangement, with slight jaundice, from which no treatment seemed to give him any relief; he was getting steadily worse, and came to me for advice. The history I obtained from him was that two years previously he underwent a very severe and sudden muscular strain, under conditions of great excitement, with the immediate consequences of faintness and prostration. Since that time he had suffered from palpitations during the exercise of his business, that of a butcher. This was followed by shortness of breath upon any exertion, headaches, bad dreams, and digestive troubles. All his symptoms, as well as the venous engorgement present, were really due to insufficiency of the aortic valve, which had, no doubt, partly given way during the violent exertion. Under rest and treatment he improved very much, and was eventually allowed to resume his business under limited conditions. Some two months later he had a slight attack of influenza, but on getting about again he felt all his old symptoms return. He then came to live temporarily near me for treatment, but a few days after his arrival was again attacked, this time very sharply, with influenza. His condition was one of an asthenic fever, the heart being especially embarrassed, the pulse becoming irregular both in force and frequency, with a dusky hue of face and a venous congestion of hands and feet. The urine became scanty and

high-coloured, and the temperature assumed a hectic character. Slight jaundice showed itself, accompanied by dyspnœa and great prostration; the face was anxious and the mind greatly depressed. The patient and his friends now made up their minds to but one possible ending. All medicines seemed worse than useless, and, as time went on, the heart failure became more pronounced.

Remembering a case of undoubted ulcerative endocarditis, under the care of Sir William Broadbent, which had much improved by the ingestion of yeasts, I was guided to the use of backérine in this case, knowing what power it possessed over microbes, though being quite unaware of the action it might have over a heart in such a plight as this; but I injected about seven o'clock one evening a full tube ($1\frac{1}{2}$ c.c.) in the region of the spleen. The reaction began about four hours afterwards, and was very violent, being accompanied by considerable delirium; at one time the patient even got out of bed; afterwards he slept, and sweated profusely. The effect of the injection was very good, for by morning the temperature had fallen to normal, but not below it, as it had done before; also medicines which seemed powerless before now began to take effect, and all the emunctory organs acted well. The system seemed to have been whipped into life, the difference in the pulse being remarkable, no trace of mitral disturbance being apparent. Perhaps I am behind the times in not being able to state that there was a difference of some 2 inches in the size of the heart, but I am quite satisfied with the other symptoms of amelioration that I observed.

A few days afterwards another injection of half a tube was given with much less reaction, and three weeks afterwards he was well enough to return to his home. In two months he was enabled to attend a little to his business. Since that time he has continued to improve, only coming to see me occasionally; indeed, I have not seen him now for four months, but I hear that, with occasional attacks of dyspnœa,

he keeps well by attending strictly to rule. In this case, I admit, the diagnosis is open to criticism ; the gravity of the condition of the man is not. A practitioner who saw him shortly before the administration of the injection told me that he never expected to see him leave the room alive, and my opinion quite coincided with his.

Considering that the bacillus of influenza, since its discovery by Pfeiffer in 1892, has become definitely known as the cause of the disease, and that it can be found in the blood of those attacked, also that in this case there was (and is still) an undoubted aortic lesion, I think it not unfair to conclude that the bacillus had here set up a bad form of endocarditis, whether ulcerative or not, very similar to that form far more often recognised as being produced by pyogenic bacteria, though certainly in this case there were no signs of emboli present. The success of this treatment in a man who otherwise seemed bound to die gives me every encouragement to resort to pure ferments in the future whenever I may meet with cases of ulcerative endocarditis in which the diagnosis is clear and undoubted, any other treatment being usually, and almost invariably, of no effect.

TYPHOID FEVER.

In this disease we have to deal with a bacillus whose habitat is at first local, in the solitary glands and agminated patches of the small intestine, though later on it invades the body through the lymphatic system. It can be found in the mesenteric glands, very numerously in the spleen, sometimes in the liver and kidneys, seldom in the blood, and very rarely in the heart. Although this seems to be a fairly wide distribution, it is much less than that of many zymotic diseases ; in this we often find the larger organs not at all infected by the presence of the bacillus, yet the typhoid bacillus has the same power of teletypton, or striking from a distance, as is possessed by the bacilli of tuberculosis and diphtheria ; conse-

quently we find the tissues of these organs subjected to cloudy swelling, and other cellular degenerations—necroses produced by the bacillary toxins. The frequency of pneumonia in cases of typhoid is probably much more due to this necrosing action having weakened the resistance of the lung tissues, and so permitted a secondary invasion, this time of the pneumococcus, than to hypostasis alone.

The period of incubation, during which time the bacillus is only exerting its influence upon the exterior or cortical part of the glands, is about fourteen days, as far as can be ascertained; after this the symptoms of zymosis begin. These symptoms are very gradual, for, of all diseases, this is the most insidious and most dishonest; frequently, indeed, the onset is so gradual and marked by so few definite symptoms that the very nature of the disease is unsuspected until grave, and sometimes fatal, symptoms suddenly manifest themselves. Patients have been known to walk into the casual room of hospitals and apply for relief from symptoms of what they expressed as a bad griping and feeling of prostration, the real mischief being perforation of the intestine, followed by death in a few hours. I well remember some few years ago a young officer on his return from shooting in Ireland seeking my advice on account of feeling languid, easily tired, and generally slack. It was in the afternoon, and his temperature was then 102·6°. I proceeded to find out the reason of it, but he objected to what he considered unnecessary fuss, telling me that he knew I could put him all right without all that. However flattering to my vanity this may have been, it was totally contrary to my practice, and it was only my refusal to prescribe for him that induced him to submit. I said to him, 'Suppose, for instance, you were suffering from typhoid and I overlooked it, what confidence could you have in me for the future?' These words, indeed, seemed like a prophecy, for examination showed him to be in the second week of typhoid fever.

Now, it is fortunate for suffering humanity that the temperature chart, when it has been kept fairly regularly, gives us a very early indication as to what the malady really is, and for the future I hope to give the patient the benefit of pure ferments whenever the temperature exhibits the pathognomonic peculiarities. We may thus scotch the bacilli before they have much damaged the glands. Within the last year we have had another valuable and confirmatory diagnostic test, signalled by Widal, whose genius discovered it, and popularized in this country by Surgeon-Majors Wright and Semple, A.M.S., at Netley.

Now, the toxins of the typhoid bacillus are so powerful that, even in those cases which recover, convalescence is always slow, sometimes painfully so. I doubt if, in the ordinary run of cases, the patient is ever quite himself again until after about two years have elapsed since the attack, not even then if the patient be young and school-work be forced on him too soon, in order to pass some examination.

One special and peculiar feature of this disease is the tendency to relapse, when the whole symptoms are gone through again. This is the more remarkable, as one attack of this disease is usually considered to confer immunity upon the system to any future invasion. To this general rule I am acquainted with three exceptions, in which a second attack occurred. In one case the second attack ended in a relapse ; in another the interval between the two attacks was twelve years, each attack being exceedingly severe and nearly costing the patient his life.

Regarding treatment, I believe that no disease rewards one so much for skilled and devoted nursing ; but it must be allied to the experience and grasp of actual morbid conditions on the part of the physician. Yet although the temperature may be lowered by packs or quinine, the powers of life sustained by proper and judicious feeding, the distressed intestines kept quiet and soothed, their peristaltic action being controlled by

opium, their contents rendered antiseptic by salol, benzo-naphthol or creasote, even the microbe partly attacked and made unhappy by nascent chlorine gas—in spite of all this, we cannot really affect the disease, we have absolutely no means of destroying the bacillus, none of neutralizing its toxins, nor any of aiding the natural defenders and safeguards of the body—the nuclein-bearing, alexin-secreting cells—in their hard fight. Can yeasts, in the form of backérine, do this? We might expect something, for we know that yeast cells *do* reinforce the natural cells, that they *do* bring auxiliary phagocytosis to the aid of the economy, but what can we say about them practically? In answer, I would refer the reader to a case reported by Dr. Cadell (*British Medical Journal*, October 29th, 1897, p. 1289). Another case, the very first in which pure ferments were ever applied by injection, was under the care of Dr. Morgan, of Seaford, which I now record in full.

A CASE OF TYPHOID FEVER TREATED BY THE INJECTION OF PURE FERMENTS.

Vere M., aged eleven years, schoolboy.

Tuesday, May 11th, 1897.—On getting up in the morning felt out of sorts, but had been perfectly well the day before, and had slept well during the night. He had no appetite for breakfast, and, as he was noticed to be dull and listless, his temperature was taken at 10 a.m.; this registered 99°. There was some headache, and the tongue was somewhat foul. The boy seemed to have the ordinary symptoms of gastric catarrh, or symptoms which are commonly termed biliousness, consequently he was kept indoors and carefully dieted. In the afternoon, feeling unable to read or play, and having a great desire for rest, he lay down on the schoolroom floor, where he was shortly found and sent to bed. He was inspected, and the skin found very hot and dry, the tongue dry and furred. The temperature had risen to 103·4°. He complained much of heaviness and

headache ; there was no sickness, no constipation, no shunning of light nor objection to noise. On the other hand, there had been no epistaxis nor any diarrhœa ; the bowels had acted naturally.

May 12*th.*—Morning temperature 101·8°. Symptoms much the same as in the afternoon of the day before. The patient was kept in bed, and was seen that morning by Dr. Morgan. The body was sponged with tepid water, and damp cloths were kept on the head, which ached and still felt heavy. Milk diet was ordered, with beef-tea twice in the day. Evening temperature 104·2°. One grain of quinine was prescribed to be given every hour.

May 13*th.*—Morning temperature 101·6°. During the night there had been a little wandering. Throughout the day the symptoms remained as on the day before. The bowels acted naturally. Evening temperature 104·2°.

May 15*th.*—Morning temperature 101°. No change in symptoms. Bowels open naturally. Evening temperature 104·4°.

May 16*th.*—Morning temperature 100·8°. The wandering delirium had become more marked during the night. During the morning the temperature rose rapidly. A wet pack was given in the afternoon, though it had no effect in bringing down the temperature, yet it seemed to check its rapid rise. Evening temperature 104·6°.

May 17*th.*—Morning temperature 101·4°. Patient very delirious all the previous night, and seemed very feeble after it, though fairly bright in his mind. The temperature soon began to rise rapidly, when a pack was prescribed, but the temperature was not reduced, nor was any action produced upon the skin. As the temperature still continued to rise, and the fever was exhausting the patient, the pack was repeated in the afternoon, with hot beef-tea and brandy administered to cause diaphoresis if possible. No effect was produced. Evening temperature 104·6°. An hour later, at

7 o'clock, it was 105°. By that time I had arrived, and we held a consultation. The symptoms noted were: The skin burning to the touch; abdomen tumid, with tenderness on pressure over the right iliac fossa; no gurgling; the area of splenic dulness decidedly increased; on the left side of the abdomen two or three slightly elevated rose-coloured spots, disappearing on pressure, but immediately reappearing on removal of the pressure. Pulse 120, soft, and of a running character. Breathing 28, short and thoracic. Lungs and heart normal. A specimen of blood was taken from the thumb in a Widal's tube, to be sent by next post to the Clinical Research Association. The quinine and packs having failed to reduce the temperature or induce skin action, and the increasing tumidity of the abdomen, combined with the great loss of strength and bad pulse, showing danger only too near, also the uncertainty engendered by the absence of the usual diarrhœa, determined us to disinfect the intestinal canal by means of salol given in powders of 5 grains each every four hours (but this could not be obtained until the following night). Feeling that time was of all importance, and judging that the pure ferment, injected hypodermically, might have the same effect, or at least somewhat the same, as I knew it to have upon the diphtheria and tubercle bacillus, I thought it right to make the experiment, also knowing it could do no harm. Dr. Morgan was also anxious to see the results. Accordingly, at 9.30 p.m. ½ c.c. of backérine was injected into the left flank in the region of the spleen.

At 10.15 the boy was asleep, but kept starting up and so hurting the side on which the injection had been made; his hands also were constantly twitching. The reaction as regards temperature was well marked.

At midnight (two and a half hours after injection) the temperature was 105·2°. He was then quite sensible and collected; he drank some milk, but afterwards became restless and not able to sleep; the mouth was dry, with much thirst.

May 18th.—At 1 a.m. he complained of aching in his left

leg and side when he moved, which prevented him from sleeping.

2 *a.m.*—Sleeping better, but breathing heavily and talking in his sleep.

2.30 *a.m.* (five hours after injection).—Temperature 106·2°.

3.30 *a.m.*—Side painful at spot of inoculation; patient had difficulty in getting off to sleep again.

4.15 *a.m.* (seven hours after injection).—Temperature, 105·8°.

5.30 *a.m.*—Patient felt pain in the left side on deep inspiration; there had been no delirium since the first sleep.

6.5 *a.m.* (eight and a half hours after injection).—Temperature 105·6°.

7.30 *a.m.* (ten hours after injection).—Temperature 104·8°. The pulse, 108, showed much more tone and tension than the previous evening, and was full and regular. The abdomen decidedly less tumid and rounded than yesterday; tenderness over spot of inoculation. Thoracic respiration 32. Only one rose-coloured spot on the abdomen remained. Milk taken three times during the night.

10 *a.m.* (twelve and a half hours after injection).—Temperature 104·4°. Patient dozed from time to time, breathing through both nostrils and keeping the mouth shut. Gugglings were occasionally heard in the abdomen, and felt by the hand placed over the right iliac fossa. The left side very tender to the touch over the area of injection, with some superficial swelling and hyperæmia. All the former rose-coloured spots had disappeared; one fresh one was noted.

1.30 *p.m.*—Temperature 104°. The patient heavy and sleepy; the side still painful, causing him to start suddenly. The body was sponged.

4 *p.m.*—Temperature 105°. The patient had just come out of a very peaceful sleep, and there appeared no reason for the rise.

6 *p.m.*—Temperature 105°. Patient seemed heavy and

drowsy, breathing heavily when asleep; complained of his legs feeling stiff.

8 *p.m.* — Temperature 105°. Salol cachets commenced. No action of the bowels since the day before.

9.30 *p.m.*—Temperature 104°. The body was sponged all over with cold water.

12 (*midnight*).—Slept since 10 p.m. very soundly, but with heavy breathing and muscular twitching, muttering and talking in his sleep. Temperature 104·4°. Face, neck and hands sponged.

May 19th, 2 *a.m.*—Temperature 103°.

6 *a.m.*—Temperature 102°.

8 *a.m.*—Temperature 102°.

The patient woke occasionally during the night, falling asleep again almost immediately, but rest disturbed by talking and starting in his sleep. Towards morning he was much brighter; the mouth was dry and parched, but, with the exception of the place of injection, he complained of no pain. Milk and Valentine's meat-juice were well partaken of during the night. Sponged with tepid water.

10 *a.m.*—Temperature 102·2°. Very bright and cheerful, with very little pain at the spot of injection. Three fresh rose-coloured spots noticed on the right side over the border of the ribs. Tongue less furred and more red.

1.30 *p.m.*—Temperature 103·2°. On account of there having been no action, an enema was administered, which produced a small loose action, causing some abdominal pain.

4 *p.m.*—Temperature 104·4° after a quiet sleep. The body was then sponged with cold water.

6 *p.m.*—Temperature 102·8°. Profuse perspiration; said he felt well, and had no pain except on breathing deeply.

8.15 *p.m.*—Temperature 102·2°. Soon went to sleep; woke at 9.45, and had a little Valentine's meat-juice. Felt comfortable and sleepy. Woke again at 10.45 feeling thirsty, had a drink of milk, and again fell asleep.

May 20th, 12 (*midnight*).—Temperature 103·4°. Woke up feeling very hot; the skin was hot and dry. Face, chest, arms, and legs sponged with cold water. At 12.40 was perspiring profusely, and then fell off to sleep, at first quietly, then with talking.

2.15 *a.m.*—Temperature 101°. Patient woke up rather startled, as if he had had an unhappy dream. Still perspiring. Went to sleep again very shortly, but kept muttering.

4.30 *a.m.*—Woke up very bright.

5.30 *a.m.*—An enema was administered with very good effect; a relaxed movement, with scybala very offensive.

6 *a.m.*—Temperature 102·4°. Slept again with a good deal of starting in the sleep.

7.15 *a.m.*—Woke up very bright, and said he felt *all right;* lips dry and cracked.

8 *a.m.*—Temperature 101·6°. Sponged all over with tepid water. Took milk and Valentine well throughout the night, also the cachets of salol at regular intervals as ordered. The night on the whole was a quiet one, and he was able to turn on to his side.

10 *a.m.*—Temperature 102·8°. Complained of hunger, and asked for something to eat. No pain in side except on turning. Arms, chest, and legs sponged with cold water, after which he slept, but awoke feeling very weak. The spots of the previous day were still present, also one or two fresh ones. A report was received from the Clinical Research Association stating that the specimen of blood sent up for examination gave the reaction for typhoid in 50 per cent. serum and 5 per cent. dilution, thus confirming the diagnosis beyond all question.

12 (*mid-day*).—Temperature 102·6°. Went to sleep, but this became disturbed, with startings and talking. Woke at 3 p.m. feeling very weak and drowsy.

3.15 *p.m.*—Temperature 103·8°. Arms, neck, and legs

sponged with cold water. Fell asleep, and woke up feeling much brighter and more cheerful.

6 *p.m.*—Temperature 102°. Slept comfortably and without talking.

8.30 *p.m.*—Temperature 103·4°. Fell asleep again, but muttering.

10.35 *p.m.*—Temperature 103°. Awoke feeling thirsty; felt hot, but the skin was moist; was sponged, after which he perspired freely.

May 21*st*, 1.30 *a.m.*—Awoke thirsty, but perspiring freely. Temperature 100°.

3.45 *a.m.*—Temperature 102°. Had been sleeping with some talking.

6 *a.m.*—Temperature 102·6°. Slept till 7 o'clock, when he awoke and seemed bright.

8 *a.m.*—Temperature 101·8°. Skin sponged with tepid water.

10.30 *a.m.*—Temperature 100·4°. Seemed cheerful; a few fresh spots were noticed under the right arm.

12 (*noon*).—Temperature 101·2°. Was sponged, after which he slept, but awoke suddenly, not knowing where he was.

5 *p.m.*—Temperature 102·8°.

6 *p.m.*—Temperature 103·8°. Sponged with cold water.

7.20 *p.m.*—Temperature 103·2°.

8 *p.m.*—Felt very hot, uncomfortable, and sleepy.

9 *p.m.*—Arms, legs, and face sponged with cold water.

9.15 *p.m.*—Temperature 100·8°. Fell asleep, and slept very quietly.

May 22*nd*, 12.30 *a.m.*—Temperature 101·4°. Awoke for a few minutes.

2.30 *a.m.*—Roused up for a minute or two; the skin felt dry and hot to the touch.

4.30 *a.m.*—Temperature 101°. Felt hot, but perspiring profusely.

5.30 *a.m.*—Awoke; enema given, with the result of a

small semi-formed stool, partly loose and one scybalous mass, not so offensive. He looked white and weak after this, and 2 drachms of brandy were given with some milk; he soon came round.

6.30 *a.m.*—Temperature 99·4°; this was taken three times to make sure. He was very bright, and trying in a feeble way to sing.

7.30 *a.m.*—Washed and sponged all over with warm water.

8 *a.m.*—Temperature 99°. Milk, barley-water, and Valentine's meat-juice taken well throughout the night; passed a very fair night, seemed cheerful, but very weak.

9.30 *a.m.*—Temperature 100·6°.

12 (*mid-day*).—Temperature 102°. Was sleepy and weak; was sponged with cold water.

2.30 *p.m.*—Temperature 102·6°. Awoke; arms, neck, and legs sponged with cold water.

4 *p.m.*—Temperature 102·4°. Awoke feeling hungry; food ordered to be increased, and to include chicken-jelly and beef-tea; action.

6 *p.m.*—Temperature 101·4°. Very cheerful; seemed better for increase of food; soon asleep.

9.40 *p.m.*—Temperature 101·6°.

12 (*midnight*).—Temperature 100·4°. Awoke, expressing himself as feeling all right; skin moist.

May 23rd.—Slept quietly, with occasional starts.

2.15 *a.m.*—Temperature 100·4°.

4.30 *a.m.*—Temperature 99·2°.

6.30 *a.m.*—Temperature 99°.

8.30 *a.m.*—Temperature 98·4°. Tongue cleaner, but breath somewhat offensive. Was washed and sponged all over with warm water. Took food (milk and meat-juice) well.

10 *a.m.*—Temperature 99·2°.

12 (*mid-day*).—Temperature 101·4°. Seemed dull and sleepy; arms, neck, and legs sponged with cold water without the effect of preventing the temperature from rising steadily.

3.30 *p.m.*—Temperature 103°. Patient was hot, restless, and refusing food; was sponged, upon which the temperature fell a little.

4.30 *p.m.*—Temperature 102·6°. Several fresh spots appeared; pulse 108, feeble and quick. No change had been made in the diet beyond a cup of cocoa at 10 a.m. I came down to see him, and a consultation was held, and as a relapse seemed impending, another hypodermic injection of ferments was agreed upon. Accordingly, ½ c.c. of backérine was administered as before, the remainder of the tube being given by the mouth (a tube contains about 1½ c.c.). The inoculation was given in the left flank, below the spot of the first. Several fresh rose-coloured spots were noticed. Some time after the injection there appeared a slight redness (local leucocytosis) for about 2 inches around the puncture.

6 *p.m.*—Temperature 102·4°. Seemed cooler and better than during the afternoon. Pulse 100, respirations 30.

8 *p.m.*—Temperature 104·4°. Fell asleep.

9 *p.m.*—Temperature 105·2°. Awoke feeling very hot and thirsty, and continued so for some time. The skin was dry and hot to the touch. Fell into a heavy sleep. Respirations 30 to 40.

11 *p.m.*—Temperature 105°. Awoke, and felt very thirsty. Complained of pain and tenderness all over the left flank; quite rational—no delirium; head dull and aching. Cold compresses applied. Soon slept again, breathing quietly.

12 (*midnight*).—Temperature 105°. Awoke feeling very thirsty, but not at all delirious. Body sponged, and cold still applied to the head.

May 24th.—Fell into a deep sleep; face flushed, breathing heavily with mouth open; respirations 34; slight twitching of right arm. Awoke at 1 a.m. very thirsty, with throat dry and sore.

2 *a.m.*—Temperature 105·2°. Awoke feeling thirsty; face and hands sponged; side painful, but dozed off into an uneasy

sleep, with movements of the legs and right arm. Breathed with his mouth shut and nostrils slightly dilated. Respirations 30.

4 *a.m.*—Temperature 104·2°. Said he felt all right. Slept again, with muttering and talking, lying on his back with both knees drawn up.

6 *a.m.*—Temperature 104·4°. Throat dry and sore. Enema administered with good result; action relaxed, with two semi-solid masses and two green pieces of mucus, or slough. Passed less urine this night than usual. Sponged.

8.15 *a.m.*—Temperature 101·6°. Went to sleep with his mouth open. Looked exhausted, and lay flat on his back. Tongue not so thickly coated—much cleaner. Abdomen and left side very tender.

10 *a.m.*—Temperature 103·4°. Seemed rather brighter, and quite clear. Very thirsty, side painful.

12 (*noon*).—Temperature 103°. No fresh spots; good perspiration.

12.40 *p.m.*—Temperature 102·6°. Awoke feeling hungry. Wanted to be read to, but soon went to sleep.

4 *p.m.*—Temperature 103·6°, but had had a good sleep, lying on his side. Tongue cleansed; later on complained of giddiness; still pain in abdomen.

6 *p.m.*—Temperature 104·2°. Looked hot and flushed, but perspired freely. Was sponged; very thirsty.

8.10 *p.m.*—Temperature 102·8°. Soon went to sleep.

10 *p.m.*—Temperature 102·8°. Free perspiration during sleep.

Midnight.—Temperature 100·8°. Abdomen around puncture tender, but he had slept well on his side. Free perspiration; breathing very quiet.

May 25th, 2 *a.m.*—Temperature 100·8°.

4 *a.m.*—Temperature 100·4°.

6·15 *a.m.*—Temperature 100°.

Only woke up just to take food, sleeping well and per-

spiring freely. Looked pale and pinched. The abdomen was tender to the touch, but not tumid. A little redness to be seen around the umbilicus, and tenderness on the left side at the point of puncture. A slight rash appeared on chest and between shoulders (sudamina). Sponged all over with warm water.

8.30 *a.m.*—Temperature 98·8°. Very cheerful.

10.30 *a.m.*—Temperature 99°.

1 *p.m.*—Temperature 99·4°. Very well all morning. Abdomen looking red, but was much less painful. Tongue cleaner, skin moist, no fresh spots. A quinine and chlorine mixture now prescribed in addition to the salol.

3 *p.m.*—Temperature 100°. Looked white and thin.

5 *p.m.*—Temperature 99·8°. Complained of hunger. The patient's voice seemed much stronger.

6 *p.m.*—Temperature 99·8°.

8.30 *p.m.*—Temperature 99·8°. Free perspiration.

10 *p.m.*—Temperature 98·4°.

May 26th, 2 *a.m.*—Temperature 98·4°.

6 *a.m.*—Temperature 98°.

8.30 *a.m.*—Temperature 97·6°.

The patient passed a very quiet, good night, only waking for nourishment. Looked very white and thin in the early morning. Abdomen still tender to the touch; but there was no redness nor any sign of bed-sores. Tongue cleaner, but lips still dry and sore. Lanoline applied.

10.30 *a.m.*—Temperature 98·2°.

12.45 *p.m.*—Temperature 98·4°. Perspiring.

4 *p.m.*—Temperature 100°. Felt very hot; then fell asleep, breathing rather quickly.

6 *p.m.*—Temperature 101°. Slept most of the afternoon, only rousing for food. He always seemed to fall into an exhausted kind of sleep whenever the temperature was rising. There had been no alteration in diet.

8 *p.m.*—Temperature 101·2°.

10 *p.m.*—Temperature 101·2°.

12 (*midnight*).—Temperature 101·4°.

May 27th, 2 *a.m.*—Temperature 101°.

4 *a.m.*—Temperature 100°.

6.30 *a.m.*—Temperature 99°.

Sleep on the whole was quiet, with occasional restlessness and heavy breathing; skin moist and perspiring; looked pinched and pale, and his eyes sunken, with dark rims round them; only awoke to take food. An enema was given; no undigested food detected; motion very offensive: liquid, with three small constipated masses. Pain and tenderness all gone from the abdomen. Passed a large quantity of urine during the last twenty-four hours.

8.30 *a.m.*—Temperature 98°.

10 *a.m.*—Temperature 98·4°.

1 *p.m.*—Temperature 99·2°.

4.25 *p.m.*—Temperature 100·4°.

6.10 *p.m.*—Temperature 100·6°.

8.30 *p.m.*—Temperature 99·4°.

Since early morning he seemed decidedly better; very cheerful when awake; slept quietly. Took food well, beef-tea, jelly, and chicken-jelly, also milk as before; a little brandy when disturbed for any reason.

10 *p.m.*—Temperature 98·8°.

12 (*midnight*).—Temperature 98°.

May 28th, 4 *a.m.*—Temperature 97·8°.

6 *a.m.*—Temperature 97·8°.

8 *a.m.*—Temperature 97·6°.

Slept peacefully all night, only rousing momentarily for food. Had no pain, but looked very pale and washed out. Skin moist. Feet slightly desquamating. Tongue white, but not thickly coated; brighter and better than at the same hour on the previous day. Partook of Valentine's meat-juice chiefly through the night.

10 *a.m.*—Temperature 98°.

8 *p.m.*—Temperature 98·4°. The temperature had remained throughout the day with very little fluctuation. The patient was very bright all day, sleeping but little, and feeling decidedly stronger; talked about getting up. Took food well.

12 (*midnight*).—Temperature 96·6°.

May 29th, 8 *a.m.*—Temperature 97·4°.

Patient slept well all night, with free perspiration. Took food well. Received an enema at 6 a.m. with much the same result as before. Salol discontinued.

From now onwards the progress to recovery was steady. Great perspirations occurred from time to time, but the strength improved daily. The temperature remained practically normal.

May 31*st.*—The chlorine medicine changed to digitalis and strychnia.

June 1*st.*—Benger's food given, and, later on, champagne. The change of food seemed to have a beneficial effect; felt continually hungry. No natural action of bowels; an enema administered every or every alternate day.

June 3*rd.*—Cocoa and arrowroot allowed as well as Benger. Perspirations less. Tongue not yet quite clean, but improved gradually until the 7th, when it became quite clean. A great increase of strength was noticed, the patient turning easily and naturally in his sleep.

June 8*th.*—Prescribed a mixture of kola-nut, strychnia, and tinct. aurantii.

June 9*th.*—Boiled bread and milk allowed, also sponge-cake with the cocoa.

June 10*th.*—Fish given. Later on bread-and-butter; he was then allowed gradually to return to solid food, after which he rapidly picked up strength, especially when he was able to be carried out into the bracing sea-air.

I am indebted for these notes to Dr. Morgan and to Miss F. J. Stone, who nursed him most devotedly. This disease was

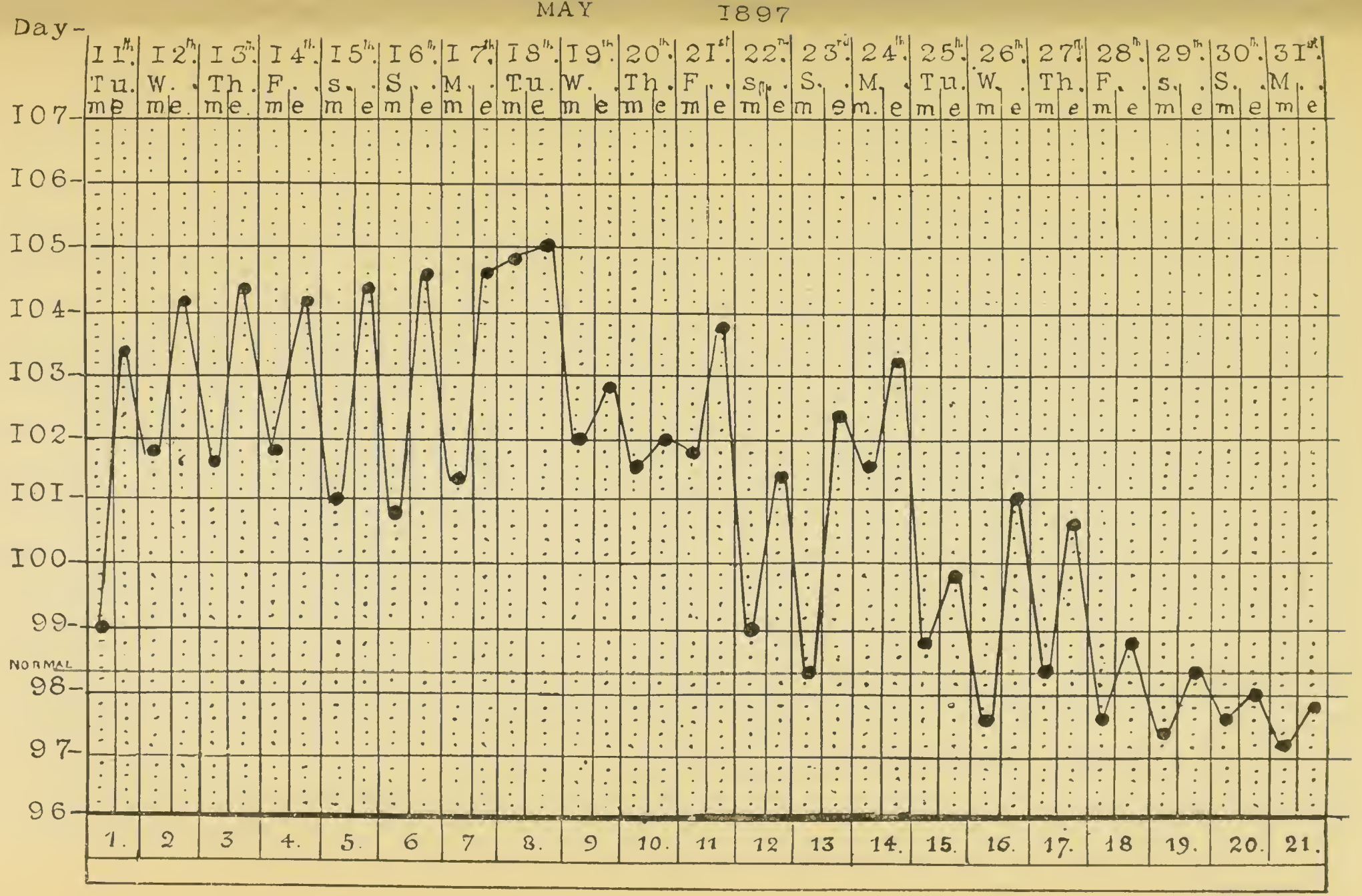
not caught at the school, whose sanitary arrangements leave nothing to be desired.

The notable features in this case were the rapid cessation of the symptoms we get to look upon as unfavourable, and the fall of temperature directly the reaction was over; also the freedom from delirium after the injections was very marked. I do not account for the seeming relapse which occurred on May 23rd, when the temperature rose suddenly, accompanied by another crop of spots and general *worse* condition of the patient. The only alteration in diet was the one cup of cocoa. It may have been that, for often quite slight causes are sufficient. From the temperature chart it would seem that there was a gradual lysis from the time of injection, when the temperature was 105°, to the normal on the sixth day afterwards, which would be the twelfth day of the disease.

It is difficult to record on paper the aspect of a patient, but those who nursed him noticed the increase of vitality given to the patient by the backérine; both of them observed the case very closely, and took most excellent notes of it. All those who were engaged in the case appreciated the power of the remedy over the disease.

At the time of deciding upon injecting these pure cultures of yeasts, I was quite unaware that typhoid fever had ever been treated by yeasts in any way, but some months afterwards I received a letter from M. de Bavay, of East Melbourne, expressing interest in the work, and giving me an account of the work he had already done in regard to typhoid fever by means of yeasts. This information was conveyed in a pamphlet reprinted from the *Australian Medical Journal*. What the author says is so interesting that I shall quote him at length.

The author begins by telling us that Dr. O'Hara brought to him for analysis a milky-looking fluid which he believed to be possessed of antiseptic and deodorizing properties,


MAY 1897
Day-
11th. Tu. me e
12th. W. me e.
13th. Th. me e.
14th. F. me e
15th. s. m e
16th. S. m e
17th. M. m e
18th. Tu. m e
19th. W. m e
20th. Th. m e
21st. F. m e
22nd. s. m e
23rd. S. m e
24th. M. m. e
25th. Tu. m e
26th. W. m e
27th. Th. m e
28th. F. m e
29th. s. m e
30th. S. m e
31st. M. m e
107
106
105
104
103
102
101
100
99
NORMAL
98
97
96
1. 2 3 4. 5. 6 7 8. 9 10. 11 12 13 14. 15. 16. 17. 18 19. 20. 21.

To face p. 208.

this fluid having escaped from the thoracic duct through an ulceration. A microscopical examination did not show the presence of any bacteria, and the ordinary cells and corpuscles of chyle were all that could be detected. Quantities of this chyle were then sown in sterilized flasks containing broth and malt extract. After twenty-four hours a growth of some organism was detected; a few hours afterwards a brisk fermentation started in those flasks which contained the malt extract. It was ascertained that the growth in the flasks containing the broth was of the same nature, and having identified both as saccharomyces, M. de Bavay assumed their presence to be due to contamination; thereupon nothing further was done.

Some months afterwards these flasks were again examined, and, to the surprise of the author, who had sown plenty of chyle, no bacteria had made their appearance in either medium. Thereupon he sowed some of these saccharomyces in fresh food solutions, and was agreeably surprised to find that they still remained very active.

To further test the power of these saccaromyces to resist the growth of bacteria, some germs of putrefaction were mixed with them. The result was that the saccharomyces developed very rapidly, whilst it was difficult to find traces of the germs of putrefaction. Some of these saccharomyces added to matter undergoing putrefaction and very foul-smelling, removed the offensive odour in a very short time. In these experiments media were, of course, used in which both organisms could develop separately. These experiments accord with those mentioned in Chapter IV., p. 72.

The author then gives a short story about yeast, all of which has been already described in earlier chapters of this work. He then goes on to say a few words about the bacillus of typhoid, limiting himself to a very few remarks, chiefly mentioning its polymorphous appearance, depending upon media, temperature, etc., and its great motility, especially in

regard to a peculiar oscillating movement very characteristic of this bacillus.

A series of experiments upon yeasts and the typhoid bacilli were now instituted.

(*a*) To ascertain the suitability of different media for the growth of typhoid bacilli. Four flasks were prepared, each containing a sterilized solution of (1) broth; (2) milk; (3) yeast-water; (4) hopped malt extract. The typhoid bacilli grew best in the broth. They grew slowly in the milk, but attained a large size. Their growth in the yeast-water was very considerably retarded, no growth appearing at all until after four days had elapsed, although the flask had been kept at a temperature of 98° F. In the hopped malt extract, no growth occurred whatever.

(*b*) To ascertain the action of yeasts on typhoid bacilli. Four flasks were partly filled with broth, to which 3 per cent. of honey had been added. These were then sterilized. No. 1 received a trace of typhoid culture; No. 2 a trace of pure yeast; No. 3 equal parts of typhoid culture and yeasts from flasks Nos. 1 and 2; No. 4 received a trace of pure yeast and, twenty-four hours afterwards, a large quantity of typhoid bacilli. The results were: In No. 1 a strong development of typhoid bacilli; in No. 2 a vigorous growth of yeast; in No. 3 no perceptible development of typhoid bacilli, but a good development of yeasts; in No. 4 a large quantity of yeast had formed before the addition of the typhoid bacilli, which did not develop.

The deduction from these experiments is that, when a liquid food suitable to the growth of both typhoid and yeast is impregnated with yeast, the typhoid bacilli are prevented from growing in it, whether added at the same time or later.

(*c*) To ascertain and compare the effects of acid and alkaline media. Two flasks of peptonized broth were prepared, No. 1 rendered alkaline by a few drops of a solution of soda; No. 2 was acid from the reaction natural to broth.

After sterilization, both flasks were impregnated with typhoid culture and maintained for a week at a temperature of 100° F. At the end of that time the typhoid had developed strongly, but not equally so in both flasks, the growth in the acid medium showing signs of ceasing, by the brightening of the fluid, on the third day, whereas the alkaline fluid remained very cloudy at the end of the week. The white growth at the bottom of the flasks differed also in quantity, the alkaline flasks containing by far the larger amount.

Experiments made upon guinea-pigs showed that largish quantities of the acid solution merely produced abscess, whereas the same quantity of alkaline solution produced death in from twenty to forty-eight hours. The result of these experiments proved that toxins were formed by the bacilli in these media, but that the quantity varied enormously, according to the alkaline or acid reaction of the media. The reason is shown by the following experiment.

(*d*) To ascertain if the results would be confirmed when sterilization by filtration was substituted for sterilization by heat. On injecting guinea-pigs with both filtered solutions, very feeble toxic reactions were manifested, although the alkaline solution had proved itself highly toxic before filtration. Repeated experiments gave the same results. It was therefore evident that the toxic substance of the alkaline solution had been retained on the other side of the filter. This observation was of great importance, as to the difference that existed between the toxicity of the alkaline and acid cultures, which is, as explained by the author, that in an alkaline medium the toxin secreted by the bacilli is continually precipitated by the alkali ; in the acid medium it remains in solution, reacts on the bacilli which have secreted it, and thereby stops their further development. (*Vide* p. 47.)

(*e*) To ascertain definitely that the poisonous matter of the alkaline solution of the last experiment was retained by the filter.

Before filtering the alkaline solution, a few drops of acid were added, enough to give it a very slightly acid reaction. The filtrate, instead of being very feebly toxic, as in the preceding experiment, had now become highly toxic, which is explained by the acid having rendered soluble the accumulated poison.

The author is of opinion that in the pre-typhoid state an abnormal alkalinity is found in the contents of the bowels, as can be proved by the excreta ; therefore, when such a state of things exists, the typhoid bacilli develop *ad libitum*, because the very substance that would interfere with their growth (typho-toxin) is precipitated as soon as formed, and removed with the excreta. To counteract this abnormal alkalinity, the author proposes the following : By the ingestion of pure yeast the reaction of the excreta will again become acid, as shown by experiments conducted on over sixty cases of typhoid ; the toxin, instead of being removed, will remain or be brought into solution, in which state it will readily be absorbed by the tissues, and not only act on the typhoid bacilli, but the tissues will little by little become so saturated by the secretion of the bacilli as to become absolutely immune, and unfit for the further existence of the bacilli. As yeast passes through the alimentary canal without suffering any change from any secretion found therein, the remedy is always ready and in a fit state to render the toxins soluble. Consequently, yeast is not the direct cause of cure, but the means of bringing about an automatic vaccination of the tissues with the produce of the growth of the typhoid bacillus.

Two other experiments were also undertaken, one to investigate the difference of effect over the typhoid bacilli by commercial and pure yeasts respectively, and the other to ascertain the exact effect typhoid fever exerted over the spleen. Both possess points of the greatest interest, but would take us too far from our present line to enter into them at present.

The author sums up as follows :

Firstly, that the action of yeast in the treatment of typhoid fever is principally due to the power which it has of secreting an acid, and to do this over and over again, by which means it is able to render acid the contents of the intestines.

Secondly, that, when such an acid reaction exists, the poison secreted by the germs reacts upon the germs themselves, and stops their growth.

Thirdly, that the action of yeast on the poison of typhoid differs according to whether it is pure or contaminated by bacteria.

Fourthly, that liquids impregnated with yeast are in a great measure protected against the depredations of the typhoid bacilli, especially if such a liquid contains fermentable sugar.

Fifthly, that these properties of yeast are not confined to one variety, but that they increase or diminish according to the power of assimilation and acid secretions of the different varieties.

Now, although I do not agree with the author in imputing the good effects of yeasts simply to their power of perpetual acid secretion, the reasons being much more complicated, and founded upon what we have already stated in previous chapters upon yeasts, their composition, attributes, and behaviour in regard to bacilli, and whilst circulating in the blood, still, I am bound to express my sense of the great addition he has made to our knowledge by his experiments; and, as these experiments were made in the year 1890, to him, M. de Bavay, belongs the honour of being the first to propose and execute the treatment of typhoid fever by yeasts. I am of opinion, however, that the treatment by subcutaneous injection will prove more efficacious by strengthening the citadel and rendering the garrison invulnerable : the ingestion of the yeasts will prove a valuable adjunct by starving

the besieger. In an earlier chapter the value of ingestion of yeasts is shown, and we habitually employ this mode of administration in other diseases in addition to treatment by injection.

Class B.

Diseases in which the pathogenic microbe has not yet been isolated :

1. The Exanthemata.
2. Whooping-cough.
3. Syphilis.

Of the two former, experiments are wanting with the exception of typhoid fever, whose bacillus we know, and about which we have already spoken at length ; but in bad cases of the remaining exanthemata and whooping-cough, which present all the characteristics of the other diseases known to be produced by formed ferments, or even in such cases as those in which ordinary treatment does not relieve, it would be well for those having the care of the sufferers to remember that, just as we possess within our own bodies a *vis medicatrix naturæ*, we have succeeded in dragging from the grand laboratory of Nature a principle which may be called the *vis adjuvans*.

Regarding the third disease on this list, I am of opinion that it will be better for many reasons to relegate its description and its special treatment in regard to pure ferments to another work.

CHAPTER XI.

DIVISION II.—DISEASES DUE TO DISTURBANCE OF THE GLYCOGENIC FUNCTIONS.

1. Furunculosis.
2. Diabetes.
3. Cancer.

Furunculosis.

This disease is characterized by the appearance of small, hard, circumscribed tumours, which are local inflammations of the skin and areolar tissue beneath it. No true abscess forms, but a circumscribed portion of the superficial fascia and deep layers of skin necrose, and are then discharged as a core. These little tumours, which are exceedingly painful, are commonly called boils, from the heat to which they give rise. They may be of any extent, from an ordinary single boil to a regular crop, or even succession of crops, of them ; they may occur at any age, in any part of the body—though some parts certainly are more favoured than others—are often exceedingly hard to get rid of, and may cause an amount of distress to the patient out of all proportion to the gravity of the ailment. A boil may be multiple though still local, causing what is known as a carbuncle or anthrax, though this must not be confounded with the charbon or anthrax of sheep and of the sorters of their wool. We have no positive evidence that the ordinary boil, or the more vigorous and fulminating

carbuncle, is caused by any particular bacillus, but experience has shown that the discharge from one boil may certainly produce another. We also know that there is some abnormal condition of the blood which allows stasis and consequent infarction, and we shall generally find that this diathesis is largely connected with a diathesis of glycosuria, quite evident by Trommer's test ; but in instances in which this has not been the case I have always found the specific gravity of the urine abnormally high, and I dare say that more delicate tests would have revealed small quantities of sugar ; a considerable diuresis is also usually present, although it often does not occur to the patient that this is so, until his attention is drawn to the fact. Certain it is that dieting the patient on diabetic principles exercises a most beneficial effect ; but as to medicines, we must say that this is one of the diseases for which so many remedies have been recommended, a fact which generally points out that very few of them are any good.

From time immemorial, that is to say, from as long as beer has been brewed to gladden the heart of the Englishman, there has existed, amongst those employed in breweries, and amongst those who were accustomed to brew their own ale—a very usual proceeding in country houses, I remember, when I was a boy—a belief that the yeast of beer was a sovereign charm against all disorders of the blood. Now, whether this was originally suggested by the goodness of the ale or not, I cannot say, but I do know that belief in its curative powers was very largely held in the provinces, which belief, although those who used it knew it not, rested on a sound basis. Country practitioners, who have been witnesses to its good effects, frequently prescribe it, and it was thus that I first learnt the power of yeasts, which led me to the further study of the reason and extent of their power ; yet yeasts have never yet been adopted into any pharmacopœia, nor have they ever received more than a casual mention in books which profess to deal with therapeutics.

It certainly seems a little odd to me, who saw yeasts administered certainly thirty years ago, and with the very best effects, too, that I should read in an annual entirely devoted to new treatment, only two years ago, that they are strongly recommended therapeutically, though I do give entire credit to M. Debouzy for his honesty in saying that he is merely bringing forward an old and popular remedy. This is also the case with myself, for I am doing the same thing with an exception, and that is a big one, that we have discovered the reason *why* the yeast does good, have found out the best kinds of yeasts to use for various purposes, also the nutriment that is most fitting for them, considering the particular work they have to do ; in addition to that, the best mode of their administration.

We find that, in furunculosis, it is seldom necessary to administer yeast by hypodermic injection, and that the old-fashioned plan of giving it raw, by the mouth, gives exceedingly good results. The usual dose when administered by the mouth is two table-spoonfuls of brewer's yeast once or twice a day, either plain or, if preferred, stirred up in either beer or porter.

Now that brewers are paying so much more attention to the quality and purity of their yeasts, we may get even better results than heretofore, yet it is not necessary, for the purpose of ingestion only, that the long and expensive process of selection and culture (absolutely necessary for inoculation) be gone through. The remedy should be steadily persevered with for three weeks or a month, but may have to be stopped or modified from time to time on account of eructations, distension from flatulence, and sometimes diarrhœa; these unpleasant symptoms can be largely prevented by giving the yeasts at a time when the stomach is free from food, especially saccharine food, which should be limited in quantity, though there is no necessity for total abstinence from it. The best local applications are poultices made with yeasts, but they must not be

heated above a temperature of 100° F., or the functional activity of the yeast may be prevented.

Diabetes.

This term is now generally understood to mean an excessive flow of urine, characterized by a notable quantity of sugar contained therein, and it is in this sense that I use the term here. The sugar may not be of a very high percentage, yet, if several quarts of urine should be voided daily, a very considerable quantity of sugar gets eliminated from the system. All gradations are seen as regards quantity, both of urine and of sugar; so it is a safer plan to judge of a patient's progress from the total quantity of sugar passed per diem, than to trust to the percentage of grains per ounce or grammes per litre. The elimination of so large an amount of liquid from the body tends to cause great dryness in all the tissues, hence we find constipation, yet with ravenous appetite, in spite of which the patient emaciates and grows unmistakably weaker; the skin is dry and irritable, the tongue and mouth constantly parched, and often cracked, the thirst most distressing. Boils and carbuncles are frequent concomitants, and changes in the retina and crystalline lens causing cataract are by no means rare complications.

The prognosis of this disease occurring in the young is quite different from that of the form of the disease which affects older people. In the former it is seldom arrested, the patient usually becoming affected with a phthisis that is soon fatal; in the latter the prognosis is much more favourable, and patients may live for many years under proper care and restrictions.

We know very little about the real causes of this elimination of sugar from the system, nor do we know very much about the pathology of the disease; but it will be a good plan first to take a glance at the sources from whence the sugar is derived. There can be but two, one of them being

from the food ingested, and the other from the carbo-hydrates locked up in the tissues; consequently the line of treatment hitherto adopted has been principally dietetic and hygienic, the former consisting of a reduction of all substances ingested which can possibly furnish sugar to the system. Even with total deprivation, we sometimes find sugar still excreted. In such cases elements of the muscular and other tissues are converted into sugar—a state of affairs which invariably ends in death. The next question to consider is, How is the sugar produced? The results of inquiries show that diabetes is not a disease, but, like jaundice, only a symptom common to several different pathological lesions.

EXPERIMENTAL DIABETES.

It has been known for many years that irritation of a spot in the floor of the fourth ventricle of the brain in animals will produce glycosuria, this particular spot being that of the vaso-motor centre, disturbance of which causes the vessels of the body to dilate, amongst them those of the liver, by which this organ receives a larger supply of blood than it is competent to deal with. Following this, we should expect that early pathological changes, simple hyperæmias, or tumours, occurring in this region of the floor of the fourth ventricle, would produce glycosuria, and our expectation is quite right. We *do* find it! We may do so also in extravasations of blood in the cervical or upper dorsal regions of the spinal cord, which appear to press upon those nerves which, arising in the medulla, do not quit the cerebro-spinal axis immediately, but run down the cord to the upper dorsal vertebræ, and then join the ganglia of the sympathetic. By taking this course they doubtless acquire a greater protection from injury. These nerves may have some control over the glycogenic function of the liver; hence, when they are pressed upon, not only does the dilatation of vessels mentioned above occur (which is the usual effect of inhibition of the sympathetic),

but it may be that the special glycogenic function of the liver is hindered temporarily or permanently. What is here meant by glycogenic function of the liver will be shortly explained.

It has also been known now for some considerable time that disease of the pancreas is exceedingly frequent as a pathological lesion in diabetes, and writers since Rokitansky's analysis of cases have called attention to this frequency, deeming it to indicate more than a casual connection with the disease; but it was not until the pancreas had been removed from the living dog, with the invariable result of producing glycosuria, that a fresh impetus was given to the study of the pathology of diabetes in this particular direction. Experimenters had found that, if only a small piece of healthy pancreas were left, then glycosuria did not occur; later on it was demonstrated that, if pieces of fresh pancreas were engrafted underneath the skin of those dogs whose pancreas had been removed, the glycosuria was arrested, which looks as if the pancreas had the power of secreting some kind of glycolytic ferment. Now, *this* Lépine actually claims to have found, and, further, maintains that it is not secreted into the duct, but enters the circulation directly. If this is the case, it would quite account for the success of the pancreatic grafts in checking the formation of sugar in the blood. This is a very important discovery, and has a practical bearing upon the treatment that we are now advocating.

CLINICAL DIABETES.

Although we have now advanced one step farther in our knowledge of the pathology of diabetes, we can easily see that it is necessary to ascertain how it is that the pancreas becomes diseased. It often happens that an inflammatory condition of the pancreas results from some previous zymotic disease, though this may have been nothing more than a seemingly mild attack of influenza. The attack, though originally

mild in its symptoms, is capable of leaving a profound depression of the system, during or following which some pre-existing or some latent disease may be roused into activity from the weakening of the resisting power of the defensive cells of the economy. The pancreas suffers in common with other organs, and is in no fit state to resist an attack of virulent bacteria. Now, we know that the pancreatic duct, about the diameter of a quill, usually opens into the duodenum at an orifice common to it and the united choledic duct; but it *may* have a separate opening into the intestine, or the duct may be double right from the pancreas up to the common orifice, which is in such cases rather larger than usual. Again, it sometimes happens that behind the head of the pancreas there exists a well-marked lobular fold, which in some cases is actually detached from the head of the pancreas. This lobe is called the lesser pancreas, and possesses a duct of its own, usually emptying itself into the main pancreatic duct, though not uncommonly opening directly into the duodenum itself, a good inch or more from the orifice of the main duct. We can now see the channels by which the pancreas discharges its secretion, and by which it may also be invaded should virulent bacteria make a determined attempt to do so. We also know that the nearest part of the pancreas to the orifice of the duct is the head, which therefore in case of bacterial invasion we should expect would be the part to suffer most. Now, necropsies show us that it *is* the head of the pancreas which is the part most disintegrated and broken down, from longer contamination with the poison.

We are aware of the important part played by the bile in preventing excess of bacterial action within the intestine; that the intestine swarms with bacteria which, when kept in check and due bounds by the action of the bile, exert a beneficent action by rendering certain articles of food capable of absorption; yet should these same bacteria find their way by some mischance into regions where no check can be met

with, they then attain a remarkable virulence. This is very clearly seen in cases of general peritonitis following perforation from appendicitis, or in perforating ulcers of the stomach or intestine. It follows, then, that in health no bacteria could pass the orifice of the common bile and pancreatic ducts without being so crippled that the leucocytes present in the pancreas would have no difficulty in dealing with them, more especially as they would be still further exhausted by having to swim against the stream of the pancreatic juice. Now, should the duct of the pancreas itself, or that of the lesser pancreases, open separately into the intestine, it would be farther away from the protective influence of the bile ; hence it may happen that, without any actual previous disease, but from lessened defensive power of the system, owing to worry, mental strain, errors of living, etc., bacteria would be the more likely to gain access to the pancreas. If this is the case in comparative health, much more so must it be in the exhausted state of our natural safeguards after acute illness, when the secretory cells have quite as much as they can do to carry on the amount of their functions absolutely necessary for existence, with little or none to spare for side-issues.

I regard the anatomical position of the pancreatic ducts as exceedingly important in relation to bacterial infection, but of course the increased risk of invasion here suggested can be nothing more than a theory until corroborated by the practical teachings of the dead-house.

That the pancreas can be infected in this way has been proved by Messrs. Charrin and Carnot, who have also induced diabetes by the injection of pathogenic microbes of different species into the pancreatic duct. Charrin had previously discovered that the amount of sugar normally present in the blood, small as it is (1 per 1,000), was materially diminished in animals that had been subjected to poisoning by the *Bacillus pyocyanicus*, and hazards a notion that this might point to a possible treatment for diabetes. As the injection of the same

microbe into the pancreatic duct can cause diabetes, the reason of the diminution of the sugar does not seem very clear, unless it so happened that a species of antitoxin had been formed, or possibly this diminution may have occurred shortly before the death of the animal, thereby resembling the disappearance of sugar from the urine, generally noticed before the onset of coma in diabetes. We will now turn some attention to the physiological digestion, sugar, starch, and the carbo-hydrates generally.

If sugar is taken into the mouth as glucose, it suffers no change until it is absorbed by the lacteals in the small intestines; but should it be taken in its more usual form of cane-sugar, or saccharose, it is immediately inverted by the saliva into glucose. Starch, whether taken as bread, potatoes, puddings, or farinaceous food of any kind, is also changed into glucose. All these sugars proceed through the stomach to the small intestine, together with other foods, as well as with those starches which have not had time to be sufficiently mixed with the saliva, a very frequent form of dyspepsia amongst lazy or silly people who do not sufficiently masticate their food. It is fortunate for such bolters that the pancreatic juice also possesses the power of converting starch into sugar.

Sugars will pass readily by osmosis through thin membranes; consequently, in people who eat much sugar, or more than their normal powers of assimilation can cope with, we find sugar free in the blood, whence it is promptly eliminated by the kidneys as an improper substance. This sugar probably finds its way into the blood directly, through the interstices *between* the outer cells of the villi of the intestine, whereas sugar in due proportion, and so in the process of normal absorption, passes into the protoplasm of the outer cells of the villi, and so through the cells themselves onwards to the interior substance of the villi, enclosed in which are other cells found lying in a network of blood and lacteal vessels. Both these outer and inner cells exert a laboratory influence

upon the sugars passing through them, and the change that takes place in the sugar by means of this influence has been compared by Pavy to that which takes place in the yeast cell.

The reader is here referred to the chapters on ferments and fermentation, wherein he will see that the yeast cell acquires from the sugar by hydration exactly what it requires for its own nutrition and propagation, splitting up this sugar in doing so into alcohol, carbonic acid, and other bodies. The protoplasm of the cells of the villi acts in a somewhat similar manner, but in this case the process is not quite the same : for, as Pavy says, the ferment action of yeast hydrates and *breaks down*, but the protoplasmic action of the cells of the villi dehydrates and *builds up*, by converting the sugar mainly into dehydrated carbo-hydrates, slightly into fats, and partly forming proteids by taking some of the nitrogen, which is always present, dissolved in the blood. For many years it was held, especially by the followers of Liebig, that the action of yeast in the production of alcohol is a catalytic action, but it is not so ; both this and the action of the villi cells is essentially a vital process. Without the vital action of the yeast protoplasm, our chemists are unable by any laboratory manipulation to produce alcohol from sugar, and I doubt if, even now, we quite know all the substances that are produced in the transformation of sugar. Still less do we know what substances are built up out of it by the intestinal villi.

A glance at the normal effect of the pancreatic juice over sugars enables us to see the probability of the glycolytic ferment of Lépine having some control over these dehydrated carbo-hydrates on their journey to the liver, considering that the pancreatic vein empties itself, through the splenic, into the portal vein, wherein it would encounter these substances. The portion of sugar which becomes transformed into fat no doubt enters the system by the vessels appointed for the purpose of

absorbing fat from the intestines, that is to say, the lacteals. The synthesized proteids and dehydrated carbo-hydrates are taken up by the veins of the villi, and finally conveyed by the portal vein into the liver, though we do not yet know the arrangements of the carbo-hydrate elements during their transit. Pavy states that he has known the amount of actual sugar present in the portal vein after a full meal of carbo-hydrate to be 4 or 5 per 1,000; but I should imagine much of this to have passed directly into the capillary veins between the villi cells, as explained above, and not through their protoplasm.

Physiological experiment has demonstrated that in the liver carbo-hydrate is converted into glycogen, which may be said to be glucose minus a molecule of water, in which state it is there stored up for future use. It is this power of storing up carbo-hydrates as glycogen, and the passing of them on into the general circulation as a reduction of glycogen in a state fit for the nutrition of the various cells of the economy, that was intended by the term 'glycogenic function of the liver,' mentioned above.

Personally, I do not think that the substance stored up is really glycogen, which, though present invariably in the liver after death, is not found in pieces of liver taken from the living subject. Unfortunately, most of the experiments have been made upon the dead subject in this direction, and in that upon the contents of the portal and hepatic veins, giving results which differ so much from those yielded by Pavy's researches on the living subject as to be as valueless as they are contradictory. It was formerly taught by Claude Bernard that glycogen became hydrated in the liver back again into glucose, according to the requirements of the body, and this opinion is still held by very many of the medical profession; but Pavy, I think, puts the case very clearly against this doctrine when he says that, if this were the case, we should invariably be glycosuric after every meal, for the urine would most assuredly throw out the sugar from the blood. The body does not want carbo-hydrate as

glucose, for this substance, when circulating in the blood, seems to act, from the symptoms it produces, as a direct poison to the tissues. Hardly an organ escapes impairment or disease. The nervous system suffers, as shown by mental and moral deterioration; the muscular system by weakness and early fatigue; the skin by its harshness, dryness, and distressing itchiness; the digestive organs by intense thirst, voracious appetite, and obstinate constipation; the lungs by chronic pneumonia and phthisis; the liver, the kidneys, and even the eyes, all feel the effect.

The question will at once be asked, If not converted into glucose for the use of the tissues, then into what is the glycogen converted? and in what state is the carbo-hydrate conveyed to the tissues? We have seen that the tissues do not want it as the poisonous glucose, and it must be confessed that the answer as to what form it must be in to be acceptable is by no means easy. There is no difficulty in hydrating glycogen into glucose, but there is an impossibility of manufacturing other substances by the dehydration of glycogen in the laboratory. The laboratory of the protoplasm has some means with which we are unacquainted of doing what is needed. We do not exactly know the true formula of this amyloid substance in the liver, which we call glycogen, as a workable term. Now, Lauth and Grimaux state that glucose can be prepared from glycerine by synthesis, and I think that it will probably be found that this glycogen, amyloid substance, or reserve of carbo-hydrate, whatever it may be, is converted by the protoplasmic laboratory into a triatomic alcohol akin to glycerine, and so used as a base for fats of different kinds; these would then be taken up by the deep lymphatics of the liver, which accompany the portal vein, and so be conveyed into the thoracic duct; therefore the secret must be hunted for in the lymphatic vessels, and not in the hepatic vein alone.

The foregoing, then, are the conditions, as far as we can

tell, under which carbo-hydrates find their way from the food to the tissues. Every man has a certain capacity for their assimilation peculiar to himself, but this capacity is not always a constant quantity, but varies considerably with age, climate, temperature, etc., so that even healthy people, if subjected to mental strain, worry, etc., whilst taking up to or near their maximum capacity of sugar, may be troubled with glycosuria from a reduction of their maximum capacity. Should the cause continue, then this maximum becomes temporarily or permanently lowered, until it is so little that what would be a very reasonable amount of sugar or starch in the diet under the ordinary conditions of life becomes too much for their powers of protoplasmic conversion ; consequently the sugar is passed unchanged into the blood, and diabetes is the result. In order to ascertain the new maximum capacity, the physician cuts off day by day a certain quantity of carbo-hydrate elements from the food of the patient until the urine shows no more than the quantity stated by physiologists to be normal. When this is found, this amount of sugar, however small it may be, is all that can be allowed to the patient. We endeavour to restore a higher maximum capacity by improved hygienic conditions, by exercise in the open air, by soothing the nervous system by codeia, morphia, or opium itself, and by the removal of any known cause, as far as can be done. By this means we may perhaps raise the capacity after a time, though it unfortunately happens that we usually see these cases after they have been going on some time, and the capacity has become permanently lowered, which means for the patient strict diet for the rest of his life.

Diet in the diabetes of young people, which is chiefly pancreatic in its pathology, is of very little use in checking the disease or averting death, for the young need saccharine food. These cases are very hopeless, and drugs are found to be of very little value. A strict diet in any form of diabetes

and at any age is sometimes so badly borne by the patient that it has perforce to be abandoned, otherwise death will only happen the quicker.

Statistics tend to show that diabetes is on the increase, but although fresh remedies are constantly being recommended, none of them have met with much success or gained general approval.

Dr. Debouzy has administered yeast by the mouth, and Cassaet also advocates this, stating that he has obtained good results from its employment, but that he is unable to form any theory upon its action.

The treatment of diabetes by the subcutaneous injection of pure ferments was partly suggested by the results of the fermentation test for the quantity of sugar present in the urine, as recommended by Sir William Roberts, partly from our knowledge, derived from experiments, that the *Saccharomyces cerevisiæ* was not debarred from exercising its functions as a ferment within the circulating fluid of the economy, when provided with fermentable matter. It simply remained to be proved whether fermentation, or a splitting up of sugar, or prevention of its formation, would occur when the fermentable matter was already provided pathologically within the blood-stream.

Experiments upon animals, artificially rendered diabetic, were not undertaken, as we knew well that injections of ferments, as long as they were absolutely pure, never did any harm ; therefore the treatment was at once tried upon a human diabetic. The ordinary reaction was experienced, neither more nor less. The blood was not mainly composed of alcohol, neither did the patient explode from the amount of carbonic acid generated. The results were that the quantity of urine, which had previously been at nearly 4 litres per diem, had sunk by the end of a week to 2 litres, beyond which quantity there was no diminution ; also the percentage of sugar had dropped from 82 grammes per litre,

at which it stood before treatment, to 45 grammes per litre. This amount was reached in about a fortnight, after two injections had been administered. No further reduction in either quantity of urine excreted or percentage of sugar was obtained, though the patient regained all his aspect of normal health. In this case, although the diabetic state was not entirely got rid of, it was evident that the maximum capacity had been exalted, for the diet had been in no way altered during this treatment to that prescribed beforehand.

Since that experiment many other cases have been treated, with similar results; and I will now give a précis of a case of my own, under the care of Dr. Hubbard, of Hemel Hempstead, which is the more valuable as it occurred in the person of one of the absolutely poor, who are unable to purchase any but the ordinary food of the working classes, and not too much even of that; hence no dieting was possible. The patient in this case was an elderly woman, sixty-eight years of age; she had had two strokes of paralysis, and the movement of the right side was very much impaired. When she came under Dr. Hubbard's care it was found that she was suffering from diabetes, with its usual train of symptoms, some of them, such as the cracked state of the lips and excoriated state of the vulva and thighs, being particularly distressing. She was then passing $5\frac{1}{2}$ pints of urine per diem, was daily getting weaker, and there was little prospect of alleviation. At Dr. Hubbard's request I went to see the case with him, and although I thought the case an admirable one for a control experiment of the ferment treatment, I was in some doubt as to whether the high tension of the arteries that the reaction was bound to produce would not precipitate an attack of apoplexy. This was put to the old lady, who was quite willing to run the risk, preferring, indeed, anything rather than the miserable state in which she then was. Accordingly, an injection of half a tube of ferments, containing next to no saccharine, but a due proportion of mineral matter, was then

and there administered over the region of the spleen. I took away with me a specimen of the urine, which analysis showed to contain a quantity of sugar equal to 187·08 grammes per diem in 3,118 c.c. of urine. The reaction was moderate, the highest temperature registering only 101·5 F. The pulse, as was expected, showed marked arterial tension. From that time the quantity of urine passed was daily measured, and a specimen of it sent to me for analysis.

The day after the injection the quantity of urine passed measured 1,530 c.c. in the twenty-four hours (instead of 3,118 c.c. as before the injection), with a quantity of 78·30 grammes of sugar (instead of 187·08 grammes). As this case will be published elsewhere, I do not now propose to enter too much into detail, but will rest satisfied in remarking that for six weeks the urine was daily measured and analyzed; that during this time she received three more injections, with the result at the end of that time that she was passing 851 c.c. of urine per diem, containing 40·8 grammes of sugar. All the distressing symptoms of excoriation, cracked lips, sore throat, and pancreatic pain and tenderness, have passed away. She was able to get up and dress herself, which she had not been able to do for eighteen months previously. During the whole of this time the patient had been kept on her ordinary diet, chiefly bread and farinaceous food, with vegetables—the sustenance of the poor. Potatoes certainly were forbidden, but I am inclined to think, from the sudden jumping up of the quantity of sugar on one or two days, that this Eve had yielded to the temptation of a 'pomme de terre.'

In this case we see some very important indications, viz., that the amount of sugar excreted daily by the kidneys was diminished from 187·08 to 40·8 grammes; also that the amount of urine excreted was notably diminished from 3,118 c.c. to 851 c.c. per diem, and that the actual percentage of sugar was also reduced, showing a considerable improvement in

the purity of the blood; and, finally, that the general and local symptoms produced by the saccharine poison were all banished.

I know of no other treatment that could produce the same results, save that perhaps of strict diet, which is always such misery to the poor sufferer, and might, as it so often does, cause anorexia, vomitings, and general loathing of the prescribed food, accompanied by increased emaciation and rapid failure of strength.

By the hypodermic administration of pure ferments, in these cases of alimentary diabetes, we undoubtedly gain time for the patient, and perhaps get him out of the diabetic habit, especially with the aid of a modified diet. In cases of pancreatic diabetes, we have here a remedy that may act in a double capacity, inasmuch as the yeast cells are able to destroy the microbes that cause the disease in the pancreas, and so effect a substitute for the glycolytic ferment of that organ, thus preventing the formation of glucose from the carbo-hydrate reserve on the one hand, and the transformation into sugar of the protoplasm of the tissue cells of the economy on the other: for we have observed that, in the normal state, proteid bodies can be synthesized from carbo-hydrates, and it is undoubted that in the pathological conditions of certain forms of diabetes these proteids are broken up and forced to render back these carbo-hydrates to the blood, this time in the form of sugar; this is true, no doubt, also as regards the fats of the body, which are probably the first to be transformed and removed. How this is done we do not know, but probably through the action of the nervous system; at least, the control of the chorda tympani nerve over the submaxillary gland would lead us by analogy to imagine it to be so.

In no case in which this remedy has been tried have we seen any ill effects from the presence of alcohol, carbonic acid, etc., in the blood due to the breaking up of the pathological sugar by the yeast cells. On the contrary, direct improve-

ment and increase of weight are noticed, probably from conversion of the alcohol into fat, a process which is often going on in the human body amongst those who consume a good deal of alcohol.

Cancer.

That our knowledge of the etiology and pathology of this terrible scourge of humanity has been greatly extended during these last few years cannot be denied for a moment. The desire of overcoming a hitherto incurable disease has stimulated the minds of men to find a means of removing this *opprobrium medicinæ*, and of relieving its unfortunate victims from the sufferings caused by it. Though the efforts of workers have resulted in many new lights being thrown upon the disease, the discovery of the true bearing of many peculiarities formerly mentioned and described, but not understood, and in greater success surgically by means of more thorough and extensive operations, still, any success by medical treatment has seemed as far off as ever.

Cancer is on the increase amongst us, although the cause for this does not seem to be very clear. It has been thought due to our conditions of increased civilization, and to many other causes, some of them ridiculous and absurd, such as the eating of tomatoes. The increase is not only in the number of cases annually, which might be accounted for by increase of population, but the percentage also has increased. It has been suggested that, owing to improved hygienic conditions, and attention to the preservation of infant life, more people reach the age at which cancer may be expected than was formerly the case, hence more cancerous individuals. If this is really so now, it will be still more so in the future, which makes the discovery of a medical remedy all the more imperative.

The cancer age, as it has been called, may be said to commence at the time when the body is fully mature and

the reproductive functions are beginning to decline. Uterine cancer is common about the age of forty, cancer of the breast a few years later. In the male sex the cancer age commences decidedly later than in the opposite sex.

Cancer is a malignant growth, usually a tumour, characterized by an extravagance in the size, shape, and proliferation of epithelial cells. It invariably originates locally in the epithelium, but does not confine itself to structures in which epithelium is normally found, but by its extravagance pushes its way into other tissues, infiltrating their elements with its cells, pushing them to one side or the other and occupying their site. This abnormal invasion may be exceedingly active in those of robust and vigorous nature, but of very little activity in old and worn-out people in whom life's stream flows but sluggishly ; hence cancers have been known to run on for even thirty years in the latter case, or to have destroyed life in a few months in the former case.

The activity of the disease is shown by the continued infiltration of the cancer cells into the surrounding tissues, but it would be well to mention here that there are no such things as typical cancer cells, for cells of exactly the same shape, size, and peculiarity are met with elsewhere in places where their presence is normal, and it is only when they are found in places where they have no business, and so give rise to destructive changes, that we can say that they constitute the cells of a cancer. These cells penetrate structures through their lymphatic spaces, in which they lie free, and by their exuberance of proliferation and growth press upon their walls and widen them out, thus causing an appearance of acini or alveoli, which communicate freely with each other, forming tunnels and labyrinths, whose walls form the stroma of the cancer, wherein lie the bloodvessels and the squeezed remains of the original structure invaded. Owing to this squeezing, and to the irritation set up by the extravagant cell proliferation, these walls inflame, and are infiltrated with small round

cells which pass between their fibres and between the bundles of the connective tissue. The result of this is the formation of fibroid tissue, with subsequent contraction, by which the bloodvessels are so pressed upon that very little blood passes, and the cancer assumes a hard, stony feel. With this lessened supply of blood there naturally comes degeneration, and, if near a surface, ulceration, which appears to be an effort of Nature to throw off the disease. By the mode of growth just described it will be noticed that there can be no capsule, and no definite limit between the cancer and the normal structures contiguous to it. If the cancer cells should be small, as they always are in the quick-growing varieties, it is more easy for them to find their way along the lymphatic channels, and the contrary holds good concerning the larger cells. In either case it is safe to conclude that there is infection up to the first gland, whose portcullis bars the road, but bars it for a while only, for a reinforcement of cells forces the outer defences of the gland, which then yields gradually from cortex to efferent vessel, and by the time this is attained the whole gland has become cancerous.

Such is, in brief outline, the history of cancer. Let us now see what should induce a few cells, a single cell, or a local group of cells, to suddenly take on such an extraordinary action. It would be beyond reason to suppose that they would do so spontaneously, and from no exciting cause. It is impossible here to enter into all the factors that have been suggested by authors as causes. Most of them possess great interest, such as heredity, age, geographical distribution, locality, etc. Each has some bearing upon certain cases, none has a universal application, though as regards conditions it may be remarked that patients removed from unfavourable environment after operations for cancer have fared better, *cæteris paribus*, as regards recurrence than those who have returned to their previous surroundings, perhaps unhygienic, or possibly possessing some attribute

favouring the growth of cancer, this having yet to be discovered.

Generally speaking, no satisfactory explanation can be given regarding the cause of the disease. Cancer has been more often than not traced to either some continued irritation or to a direct blow. As an instance of the former we may cite epithelioma which occurs on the lips of smokers who use a clay pipe, the warm, porous stem of which sticks to the moist mucous membrane, so that it is torn away every time the pipe is removed. An ordinary wart, mole, or little papillomatous growth on a scar may take on cancerous action from being constantly irritated and fiddled with. Most medical men have been told the story from the mother of a child kicking her violently in the breast, either in anger or in play. Another story has often been told me when in Wiltshire, that the sufferer remembered leaning heavily with her breast on the handle of a hay-rake, and that ever since then the breast had felt more or less tender, until the time when a distinct swelling was noticed. Dr. Unoneau has pointed out that in cancer of the œsophagus the disease invariably occurs in one of three places, either at a point behind the cricoid cartilage, or at another where the œsophagus passes behind the bifurcation of the trachea, or a third just where it enters the opening in the diaphragm. Now, it is precisely at these places that we find there is a narrowing of the tube, and consequently greater irritation from friction, especially among people who are silly and careless enough to bolt their food. Whether the subjacent tissues are weakened by irritation or blows, and therefore cannot resist the invasion of the epithelial columns, we are not yet in a position to say.

It has been remarked that attendants upon those suffering from cancer have themselves sooner or later developed the disease, and this whether the two have been blood relations, related by matrimonial ties, or totally unrelated. An example of the last, which came under my observation a few years ago,

is a very forcible illustration. The proprietress of a large school for girls retired, and went to live in a country village, where she built herself a house. About a year afterwards she developed cancer, and was constantly attended by one who had been a governess for many years in the school. The proprietress died, and bequeathed the house to the governess, who continued to reside there, but very soon was taken with the same disease as her old friend, from which she also died. Besides cases like this, it has been noticed that cases of what has been called contact cancer have occurred not infrequently ; by this term is meant that one local growth has seemingly excited another similar one in healthy tissues frequently in contact with it, such as a growth on one lip provoking a corresponding growth on the other at the opposed part. Again, cases have been known to occur among succeeding tenants of certain houses ; latterly the medical papers have been very full of reports of such cancer-houses.

These several considerations have led to the idea that cancer may, after all, be due to some living force from the outside, either bacteria or protozoa, as in malaria. This idea is considerably strengthened by the discovery that other diseases, such as actinomycosis, or the wooden tongue of cattle, which also occasionally attacks mankind, always formerly regarded as a form of cancer, is a disease really due to the ray fungus, or actinomyces. Since the beginning of this decade an enthusiastic search has been made for the possible micro-organism, together with repeated experiments upon the inoculability of cancer from animal to animal of the same species, and from an animal of one species to that of another. The hunt for a micro-organism resulted in the statement by Kiibasoff that he had discovered a special rod-shaped bacterium as the cause of all cancers, in a claim by Scheurten to the discovery of the spores of bacilli, in Schill's double-pointed bacillus, in Lampiasi's bacillus, etc., yet no subsequent observer was ever able to corroborate these dis-

coveries. The next interesting communication was made by Dr. W. Russell, who discovered bodies in the cells of cancers which stain brilliantly, and have therefore been named fuchsin bodies. These, he is persuaded, have a very decided influence upon the cause of cancer; he describes them as propagating by budding, and so imagines them to be related to the saccharomyces tribe. These observations have been confirmed by others, who have supposed them to be protozoa of the form coccidium. The good work has been carried on by Jackson-Clarke, Ruffer, and Plimmer, and others, yet absolute conviction is not yet brought home to the majority. Russell himself has found his fuchsin bodies in other structures, both physiological and pathological; also skilful manipulators and bacteriologists tell me that they can produce similar appearances in almost any tissues by a skilful handling of the stains. Let us just take a glance at the difficulties that Robert Koch had to overcome before he could demonstrate the tubercle bacillus without possible refutation, and the many scientific sniffings that ensued. Because we can now make preparations of this bacillus by the dozen in a few minutes, it seems that the process must always have been known, and the same remark applies to its cultures; thus we are likely to forget all the hard preliminary work.

It may be in the future, that those who are now students will read with some amusement all our gropings in the dark. It is such gropings, however, that gradually sweep away the darkness; let us, then, grope on. It would appear that a cause of this disease by micro-organisms is the only one that can fit in with all the facts known about it; the peculiar cachexia of cancer, which is so pathognomonic, can be explained as due to toxins; any other explanation is difficult.

Professor Foa, at the Medical Congress in Rome, gave a most admirable review of the work done by different observers, and described these cancer bodies to be endo-protoplasmic bodies, paranuclear, and enclosed by a double-outlined capsule;

they consist of thin protoplasm and a small central body; when the body is large, the protoplasm on the surface appears puckered and festooned, the whole appearing very much like a medlar fruit. These parasites are of smaller size than a red corpuscle; they invade the epithelial cells, and push the nucleus to one side; should a leucocyte or more than one enter the invaded cell, then the protozoon appears to undergo coagulation necrosis. These cancer bodies are so well described in Greene's 'Pathology,' and in works by the various investigators already referred to, that further information concerning them need not be given here.

Experiments made to ascertain the inoculability of cancer have given very contradictory results. No doubt the disease has been communicated to animals of the same species, but it has never yet been communicated from man to animals. What is really required in order to prove cancer to be an infectious or contagious disease is that we should be able to separate the infective material or ferment, and reproduce the disease with this at will. If the infective material should really prove to be a protozoon, this work will be difficult, because, although we know very well that malaria is due to the action of protozoa, it is not in our power to reproduce the disease or to make cultures of the parasite outside the body.

It is worthy of remark that the more successful cases of inoculation of cancer in one animal from another occurred in animals that were about the cancer age, younger animals not being affected at all. This fact leads us on to consider the question of the *terrain*, or medium of predilection: for it is well known that every microbe has its own peculiar fancy, hence the difficulty of cultivating some of them until the pabulum they prefer has been found out; it may be therefore that, unless the microbe of cancer is placed in surroundings that are very favourable to it, it will not grow. We must in consequence try to find out what these conditions may be,

because it is upon them that the whole series of phenomena depend, whether the cause be microbic or not.

Now, we have already stated that the cancer age is a mature age, at a time when the processes of assimilation and waste are about evenly balanced. It follows, then, that any hereditary or acquired weakness would be likely to show itself about that period, from diminution of cellular activity. The economy, therefore, is not equal to the dietetic strains often put upon it, that it could perfectly well endure when the phenomena of growth required a large amount of ingested food ; the elasticity of all organs is considerably diminished, consequently their functions are easily disturbed.

We can see for ourselves that the urine of cancerous people contains much less urea than that of people in health, showing a lessened excretion of nitrogenous matter. This matter, which should have been excreted, is probably used up by the neoplasm in the manufacture of its new cells ; hence some physicians have interdicted animal meat as diet, in the hope of checking this undue cell proliferation.

Passing on to the heat-producers of the economy, we find that the favourite points of attack in cancer are those which are the more richly endowed with potential sugar—the uterus, breast, liver, stomach, etc. These two facts taken in conjunction with that often noticed, that the actual point of the commencement of cancer is situated in a cicatrix, or induration, we may safely conclude that disturbance of nutrition is a very potent factor in the preparation of the *terrain* for the reception of the cancer germ, whatever that may be.

It is quite possible that, in these points of predilection or chosen spots, potential glucose, as glycogen, or some glucoside, may be stored up in greater quantity than is normal, owing to a perverted nutrition ; and this, with the excess of circulating proteids, so feeds the invading cells, lying in the lymph spaces, with such a superabundance of food that they grow to an enormous size, and with tremendous rapidity, adopting all

sorts of odd shapes from pressure upon one another in the exuberance of their growth. Granting the theory of infection by protozoa to be true, it would follow that these well-fed cells would resemble very strongly the well-fed caterpillar, into whose body the ichneumon fly deposits its eggs, which eventually hatch out and destroy their host; in like manner may the protozoa take up their abode in the fat cells mentioned. With such an array against them, what can the poor leucocytes do? They do their best, for we see them after they have penetrated the epithelial cells in order to get at their enemy. We also see that this enemy, in such cases, has to succumb, yet the growth is so rapid, and the leucocytes probably few and debilitated, that their opposition to the march of the disease is usually of a very feeble character.

From these premises, the rational medical treatment would appear to be, first, to lessen the amount of ingested nitrogen, and, secondly, to break up the glycogen within the area of invasion. That this glycogenous condition is a point of real moment is made clear by M. Brault's analysis of eighty-one cases of cancer and other neoplasms, which gave results that they not only contained a notable and sometimes exaggerated quantity of glycogen, but that the tumour was directly the more malignant clinically in proportion to the quantity of glycogen contained in it; hence cancer has been termed by De Backer to be the result of a 'local diabetes,' and it is on this account that I have included cancer among those diseases which are due to disturbance of the glycogenic function, or perhaps it would be more correct to say the distribution of carbo-hydrates to the tissues.

How, then, can we fulfil the two objects of treatment above mentioned? The first may be accomplished by lessening the amount of animal food—by allowing no brown meat, or what is commonly termed 'butcher's meat.' The second may be carried out by the injection of pure ferments, which can

and will break up the glycogen, and so starve the growth. Furthermore, again granting that the protozoon theory is correct, it is perfectly possible, theoretically, considering the small size of the protozoa, for a vigorous young yeast cell, acquiring its nourishment *in situ* by the saccharine of the growth, to inglobe and digest the invading protozoon.

It will be interesting at this stage to mention once again how pure ferments first came to be used therapeutically in cancer. Among the numerous guinea-pigs used for the experiments in ascertaining the harmfulness or innocuity of pure yeasts, when injected into healthy animals, and the dose that it would be best to employ, it was found that although the little creatures, male and female, lived freely together, from which progeny might reasonably be often expected (these animals being very free breeders), yet this very seldom happened, and that when female guinea-pigs became likely to produce little ones, these either arrived before their time, or, if born at full term, they were seldom fully developed, and died shortly after birth.

It was deduced from this that the ferments acted upon the glycogen normally present in the uterus and ovaries, by reducing it and causing its absorption, whereby the functions of those organs became altered or annulled. Regarding the fact of the terrible frequency of cancer in the uterus among women, and how rapidly this disease increases during pregnancy (a time when the uterus is heavily charged with glycogen), the idea arose that as the glycogen present in the normal condition of the uterus could be broken up, perhaps its physiological and pathological increase might also be reduced, and cancer arrested or cured. What has just been said about the uterus in pregnancy applies with equal force to the breast during the period of lactation ; mammary cancer in such cases acquires an inordinate activity, as if 'lashed on' ('le cancer reçoit un coup de fouet'—De Backer) from the extra amount of glycogen, frequently evidenced by a

glycosuria which, according to Ney, is the normal condition of women during suckling.

The mode of application varies somewhat with the conditions of the case. It is not much good injecting the ferments into the mass of the tumour when it is very hard, unless one were lucky enough to hit off one of the spaces in which the cells lie ; also it is not the spot of activity, but of commencing degeneration. The best places are in the tissues immediately surrounding the growth, in the direction of the lymphatics passing towards the tumour, as well as in those passing away from it. I am inclined to begin the treatment with a full dose, one tubeful, which may, however, be injected in two separate places. This should be repeated in a week and in a different spot.

For epithelioma of the lip, very little is required at a time—a few drops only ; this may be given in the cheek or chin, near the angle of the jaw. For internal cancer, it is as well to keep as near the tumour as possible without actually penetrating it, the great point being to hit off the zone of active cell proliferation, or places may be chosen at a distance if the lymphatics lead to regions near. In uterine cancer, the iliac regions, the buttocks, and Scarpa's triangle are good places ; in all cases it is better to inject as deeply as possible, and not only subcutaneously, but, of course, anatomical considerations must be borne in mind in some places, such as Scarpa's triangle.

As a dressing for cancerous ulcers, and, indeed, foul ulcers of any kind, syphilitic, varicose, etc., nothing gives such good results as a bi-diurnal dusting with a dried preparation of yeast. It was found exceedingly difficult to prepare a yeast sufficiently dry to keep sound, and yet retain its properties ; but, after many experiments in the laboratory, we have succeeded in preparing a 'poudre cicatrisante' which may be blown on to an ulcer through a paper tube, a common pea-shooter, or insufflated by a little apparatus made

for the purpose. This powder is exceedingly valuable for insufflating the throat and nose of children suffering from diphtheria, especially when there may be a difficulty in the application of liquids. The powder adheres to the membrane and destroys it by digestion; it is not nasty, and children have no objection to it. For cancer, the dusting should only be exceedingly light, and, after it has been left for an hour, warm sea or salt water on rags makes a very soothing dressing. The poudre cicatrisante should be kept air-tight in a dry cool place, as warmth and moisture, or both together, would very soon lead to attempted proliferation and degeneration. For reports of cases of cancer the reader is referred to De Backer's writings,* in which a selection of cases will be found. My cases, both of this and of the other diseases mentioned in this work, will be afterwards published in monographs. I regard as cases amenable to treatment, and in which I have seen more favourable results, those of secondary or inoperable cancer of the breast, cancer of the stomach, uterus, and of the rectum; of epithelioma of the lip I have only one case, which is doing well. Cancer of the tongue and of the throat I regard as offering very little hope of success; but, then, it is only fair to say that such cases have only been brought to me when far gone. Even in cases in which the disease has not been arrested, I have found, with one or two rare exceptions, that the terrible pain has been very considerably relieved.

In concluding this subject, I may mention that all I have written is without any reference at all to surgery. Looking at cancer as being a disease of local origin, I am the more and more convinced of the necessity for early, free, and extended surgical interference, which will probably eradicate the disease entirely. Should there be any doubt as to diagnosis, an exploratory incision can do no harm, and is recommended by the best surgeons. The greatest mistake

* 'De la Cancérose et son Traitement par les Ferments purs,' par le Docteur De Backer, 1897.

is to wait until the symptoms become only too obvious. Any patient who shuns an early operation is either exceedingly foolish or very ill-advised. Certainly, none of us like the idea of being maimed, but even that is a very good exchange for death by cancer.

It is in those cases of recurrence, or in internal cancer, in which surgery is powerless, that we more than hope, and may reasonably expect, many cures in the future. The treatment is a new one, but founded on solid grounds; being new, it has much before it, also much may be evolved from it in the future. If, however, even at the commencement, we can *cure* only a few of those who could not otherwise have been cured, we shall at least have done some good, which is the true aim and object of the profession to which we feel proud to belong.

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Properties. A green extract made of the expressed juice of the fresh leaves and young branches; has a bitter taste. Active principles: atropine.

Use. Used externally as local anodyne and antispasmodic; internally as a cerebral, spinal, cardiac, and pulmonary sedative; anhydrotic and antispasmodic.

Therapeutics. Useful in the treatment of anal fissure, tenesmus, and perniones; pertussis, laryngismus stridulus, asthma, dysentery, follicular enteritis, spastic constipation, colic, and lead colic. Has the same mydriatic action as atropine. Children bear belladonna better than adults.

Dose.
gr. $\frac{1}{60}$ to $\frac{1}{30}$ (0·001–0·002) to a child 3 to 4 months old;
gr. $\frac{1}{30}$ to $\frac{1}{15}$ (0·002–0·004) to a child 4 to 6 months old;
gr. $\frac{1}{8}$ (0·008) to a child 1 year old;
gr. $\frac{1}{4}$ (0·016) 2 to 3 years old;
gr. $\frac{1}{2}$ (0·03) ,, of 5 years, for an initial dose; the doses to be increased slowly.

Highest doses pro die:
gr. $\frac{1}{6}$ (0·01) for a child 6 months old;
gr. $\frac{3}{8}$ (0·024) ,, 1 year old;
gr. $\frac{1}{2}$ (0·03) ,, 2 years old;
gr. $\frac{3}{4}$ to 1 (0·048–0·06) for a child 4 years old;
gr. 1 to $1\frac{1}{2}$ (0·06–0·1) for a child 5 to 6 years old.

After 5 years of age the tolerance of belladonna diminishes gradually.

Incompatibles. The chief incompatibles are tannic acids and tannates.

Correction of Taste. The taste of gr. $\frac{1}{8}$ of the extract is disguised by min. 2 of spirit. chloroform. or min. 5 of syr. aurantii.

Formulæ.

℞. Ext. belladonn., gr. $\frac{1}{8}$.
Spir. chlorof., min. 2.
Aq. destillat., ad dr. 1.
S.: Three times a day.
For a child 1 year old.
(Hospital for Sick Children.)

℞. Ext. belladonn. gr. $\frac{1}{6}$ to $\frac{1}{2}$.
Butyr. cacao, dr. $\frac{1}{2}$.
S.: Suppository.
For a child 1 to 3 years old.
Tenesmus, fissura ani.

℞. Ext. belladonn., gr. $\frac{2}{3}$.
Ferr. carbon. sacch., gr. 15.
Sacch. lactis, dr. $\frac{1}{2}$.
M. f. p. divide in part. æqual. No. 10.
S.: One powder at bedtime.
For a child 4 years old.

Antidotes. Morphine, eserine, pilocarpine.